COGRENO MONOGRAPH

Part I – Disease introduction – Post stroke dementia

Dementia

Age related dementia is an irreversible condition that results in progressive cognitive decline. It has emerged as one of the leading health problems of our time. Advances in prevention and healthcare have increased life expectancy and produced a shift in the burden of disease worldwide. Thus, non-communicable diseases, including dementia, have been recognized for the first time as the major threat to the world population. The World Health Organization estimates that 35.6 million people live with dementia, a number that is anticipated to triple by 2050. Every year 7.7 million new cases of dementia are diagnosed, imposing a tremendous burden on families, the primary caregivers, and financial cost to society.[1]

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Main causes of dementia

The term dementia encompasses a loss of various brain functions severe enough to interfere with the affected person's activities of daily living. There are various causes of dementia, the most common being Alzheimer's disease (Table 1).[2]

Table 1: Types of dementia[2]	
Alzheimer's disease	The hallmarks of Alzheimer's disease are excessive accumulations of a fragmented protein called beta amyloid, known as plaques, and abnormally twisted tau proteins, or 'tangles'.
Vascular dementia	In vascular dementia, there is evidence of brain damage caused by deficient blood supply to the brain.
Lewy body disease and Parkinson's disease dementia	In Lewy body disease and Parkinson's disease dementia, there is abnormal clumping of a protein called alpha-synuclein.
Dementia due to Huntington's disease	Dementia may also be caused by certain genetic conditions, such as Huntington's disease, where the defective genes can cause abnormalities in brain proteins. These forms of dementia may be broadly described as neurodegenerative, since they lead to progressive nerve cell death and a decline in the person's condition.
Other causes of dementia	Other causes of dementia include brain damage because of chronic alcoholism, repeated head injury, infections such as human immunodeficiency virus (HIV) and neurosyphilis, excessive fluid accumulation in the brain (normal pressure hydrocephalus) and certain metabolic disorders, such as calcium and sodium abnormalities.

The common causes of dementia include vascular risk factors and cerebrovascular disease. Common risk factors for vascular dementia and Alzheimer's disease, as well as frequent coexistence of these pathologies in cognitively impaired older people, suggests convergence of the etiology, prevention and management of the commonest dementias affecting older people. Considering this understanding, the cognitive impairment associated with cerebrovascular disease is an increasingly important and recognized area of the medicine of older people. The diagnosis of brain vascular disease is important because of the potential to improve clinical outcomes through clear diagnosis, enhanced control of risk factors, lifestyle interventions and secondary prevention.[3]

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Vascular cognitive impairment

Vascular cognitive impairment (VCI) is a syndrome that encompasses all cognitive disorders associated with vascular disease. These cognitive disorders range from mild to severe cognitive impairment including vascular dementia (VaD). There is involvement of at least one cognitive domain in the mild form of the disorder, whereas multiple cognitive domains are involved with more severe forms of the disorder. In the past, different terminologies have been used to describe the association of vascular brain injury and cognitive problems. These include but are not limited to multi-infarct dementia (MID), post-stroke dementia and VaD.[4]

Globally, the occurrence of ischemic strokes is almost 4-fold greater than hemorrhagic strokes. According to current evidence, that 25–30% of ischemic stroke survivors develop immediate or delayed vascular cognitive impairment (VCI) or vascular dementia (VaD). Dementia after stroke injury may include all types of cognitive disorders.[5]

Epidemiology

Cognitive impairment occurs after stroke in 6–41.3% of patients but can also arise from covert CVD; a recent study found an incidence of dementia after stroke in 23.9% over an average follow-up of 3.8 years. In clinical studies, the prevalence of VCI/ VaD ranges from 4.5 to 39%, in Western memory clinic- and population-based series averages 8–15.8%.[6]

Pathophysiology

Some of the common and important pathologies in patients with VCI are white matter lesions, brain infarcts, and hemorrhages which result in tissue damage and loss. Macroscopic

or microscopic infarcts could contribute to VCI. However, the precise number of infarcts required to cause VCI is unknown. Number, volume and location of infarcts are predictors of VCI, neuropathological criteria for the diagnosis of VCI. VCI patients are characterized by a disruption and malfunction in the blood–brain barrier and neurovascular unit. There are alterations in microvascular structures such as thickening of basement members, tortuosity of blood vessels and reduction in their number, changes in arterioles and lipohylinosis of deep penetrating arteries in patients with VCI. The disruption of the blood–brain barrier may be associated with an inflammatory response and can result in impaired cerebral autoregulation. There is a potential role of matrix metalloproteinases in this process, and these enzymes are increased in the cerebrospinal fluid in patients with VCI (Figure 1).[4]

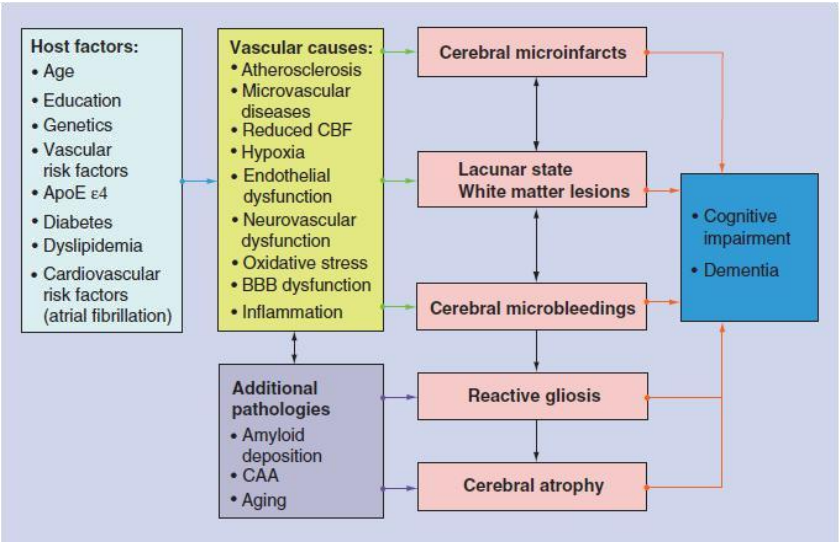

Figure 1: Schematic interplay of pathogenic factors causing vascular cognitive impairment/dementia.[6]

Risk Factors

Awareness of VCI is important as many of its risk factors are modifiable (Figure 2).[4]

Non-Modifiable risk factors	Modifiable Risk Factors
• Age • Sex • Genetic factors	• Diet • Physical activity • Hypertension • Hyperglycemia and Hypoglycemia • Hyperlipidemia • Metabolic Syndrome • Smoking • Alcohol Consumption • Carotid and intracranial atherosclerosis • Atrial Fibrillation • Peripheral Vascular Disease

Figure 2: Risk factors for Vascular cognitive impairment

Clinical Presentation of VCI

The clinical presentation of VCI varies. VCI can present with mild deficits affecting one cognitive domain or advanced cognitive impairment (i.e., dementia). Size and location of WMLs, ischemic and hemorrhagic strokes are associated with varying clinical presentation in these patients. Many of these patients have difficulty with executive function which may include difficulty with planning, executions of tasks in their routine daily life, and switching from one work task to another.[4]

Interventions

Prevention of stroke recurrence and stroke severity through optimal acute treatment and intensive secondary prevention is the best way to prevent PSD. Intravenous and intra-arterial interventions (if indicated), treatment in the stroke unit including prevention of complications, and early rehabilitation are thought to limit the damage from the stroke lesion and improve outcome. Secondary prevention includes medical interventions and lifestyle modification. Cognitive function can benefit from treatment of neuropsychiatric symptoms like depression, apathy, and anxiety, as well as cognitive training/stimulation.[7]

Pharmacological interventions for prevention of PSD

Blood pressure lowering

Blood pressure lowering may have some beneficial effects on cognitive decline. Hypertension treatment after stroke preserves cognition through prevention of recurrent

stroke, but it is not yet clear whether it prevents cognitive decline through other mechanisms.[7]

Statin treatment

Statin therapy in secondary stroke prevention has shown an effect on new vascular events but only marginally reduces the risk of stroke recurrence. Statins lower LDL cholesterol and may have a beneficial effect on platelet function, endothelial activity, and inflammation. No study has tested the effect of statins on cognition in patients with previous stroke.[7]

Other potential Pharmacologic interventions

Many therapeutic strategies have been developed for neuroprotection in acute stroke .[7]

Potential Pharmcologic interventions for vascular cognitive impairment
Nitric oxide donors
Acetylcholinesterase inhibitors
Memantine
Cerebrolysin
Selective serotonin reuptake inhibitors
Citicoline
Phosphodiesterase-3
Anti-inflammatory agents
BBB modulators
Endothelin antagonist
Flavonoids
Immunosuppressive agents
Peroxisome proliferator-activated receptor gamma
antagonists Sympathomimetics
Xanthine oxidase
inhibitors Prostacylin
Antidepressants
Neurotrophic agents
Prostacylin
Gingko biloba extract Egb-761

Lifestyle interventions

Multifactorial interventions

Most vascular risk factors are modifiable. Lifestyle modifications include physical exercise, healthy diet, moderate alcohol consumption, and smoking cessation. Multimodal lifestyle interventions have been successful in changing the lifestyle habits of stroke survivors.[7]

Lifestyle modifications for the prevention of post-stroke dementia include physical exercise, healthy diet, moderate alcohol consumption, and smoking cessation

Physical interventions

Increased physical activity after stroke improves cognitive performance. Exercise training is standard for cardiovascular disease management, and cardiac rehabilitation was shown to improve cognitive performance in several studies. Sharing the same risk factors as stroke, brain rehabilitation including exercise might be a right strategy in future stroke care, supported by papers published over the past 2 years.[7]

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Cognitive training

Cognitive rehabilitation is a complex therapeutic intervention aiming to improve cognitive function after stroke; at present, the approached strategies are individual remediation therapy with a neuropsychologist, group-based training, and computer cognitive training. Cognitive rehabilitation plays an integral role in stroke multidisciplinary rehabilitation and should be started shortly after stroke onset, with effectiveness both in the post-acute period and a few years after stroke.[7]

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Non-invasive brain stimulation

Non-invasive brain stimulation techniques, including repetitive transcranial magnetic stimulation and transcranial direct current stimulation, have been reported to improve functional status of stroke patients through modulation of the excitability of cortical circuits.[7]

Actovegin

Natural biological products, such as actovegin, may have beneficial effects in the restorative phase of ischemia. Actovegin has been shown to have effects on some cellular processes in the aging brain and recent experimental studies revealed actovegin to play a role in neuroprotective mechanisms.[7]

Piracetam in cognitive impairment

Piracetam is a drug that may enhance memory and other intellectual functions through mechanisms which are ill-understood and still debated.

Piracetam (2-oxo-1-pyrrolidine acetamide) was the first of the "nootropic" drugs that acts against external traumatic factors such as hypoxia, electroconvulsive therapy or barbiturate poisoning. It is a cyclic derivative of gamma-aminobutyric acid (GABA) that can cross the blood-brain barrier and is selectively concentrated in brain cortex. Even at high doses it has no sedative, stimulant, locomotor or autonomic effects. At low dosage, piracetam might produce cognitive enhancement by increasing oxygen and glucose utilization through adenosine triphosphate (ATP) energy pathways. At higher dosage, it opposes platelet aggregation and has rheological and antithrombotic effects.

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Although not yet known in detail, it appears that one of piracetam's mechanisms of action may be through muscarinic cholinergic activity, although other neurotransmitters may be involved. There are reports of an effect of piracetam on dopamine metabolism. Piracetam appears to be well tolerated in low doses (up to 10 g daily) and does not interact with antibiotics, anticonvulsants, analgesics, antidepressants, antihypertensives or hormone replacement therapy (HRT). Beneficial effects of piracetam on learning and memory have been demonstrated in several animal studies including some on older animals.[8]

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Gingko biloba in Cognitive impairment

Medicinal products derived from the maidenhair tree, Ginkgo biloba, are some of the most widely used of any plant-based products. The active components of Ginkgo biloba consist of flavonoids, terpenoids, and terpene lactones (ginkgolides and bilobalide).

The main use of Ginkgo biloba is in the treatment of cerebral dysfunction. Its properties may include protection of neuronal and myocardial cells against ischemia and reperfusion injury. The medicinal properties of Ginkgo biloba may be attributed to a combination of effects and that it acts by increasing blood supply by dilating blood vessels, reducing blood viscosity, by modification of neurotransmitter systems, and by reducing the density of oxygen free radicals.

Ginkgo biloba is recommended for age-related cognitive decline and for slowing the progress of neurodegenerative disorders such as Alzheimer's disease and for other forms of dementia. Many clinical trials have been conducted to assess these potential properties and several reviews of the results have been published but there is still no compelling evidence of the efficacy of Ginkgo biloba for cerebral function.[9]

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Vinpocetine in Cognitive impairment

A cerebrovascular accident, or stroke, is defined as the abrupt onset of a neurological deficit, which can be due to ischemia. Cerebral ischemia is caused by a reduction in blood flow that thereby decreases cerebral metabolism. Chronic cerebral hypoperfusion leads to irreversible brain damage and plays an important role in the development of certain types of dementia. Vinpocetine, chemically known as ethyl apovincaminate, is a vinca alkaloid that

Vinpocetine, chemically known as ethyl apovincaminate, is a vinca alkaloid that exhibits cerebral blood-flow enhancing and neuroprotective effects

exhibits cerebral blood-flow enhancing and neuroprotective effects. Non-clinical and clinical studies have suggested multiple mechanisms responsible for the beneficial neuroprotective effects of vinpocetine. As no significant side effects related to vinpocetine treatment have been reported, it is safe for long-term use. This vasoactive alkaloid is widely marketed as a supplement for vasodilation and as a nootropic for the improvement of memory.[10]

Emergence of combined treatment for dementia

Dementia has become a worldwide public health concern. The World Alzheimer Report warns that 46.8 million people worldwide are living with this debilitating illness in 2015, with an estimated increase to 131.5 million by 2050. Dementia has a titanic economic impact, with an 818-billion-dollar total estimated worldwide cost that will eclipse a trillion dollars by 2018 and increase to 2 trillion dollars by 2030.[11]

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Extracts of ginkgo biloba have been broadly prescribed toward advance symptoms of cognitive dysfunction ranging in severity from mild memory loss to dementia also; in delaying the development of dementia; ginkgo biloba has been encouraged commercially as a smart medicine to augment the brain function of healthy people. Piracetam is a no tropic remedy correlated to inhibitory γ-aminobutyric acid (GABA) neurotransmitter. Piracetam may be the initial agent acting on cognitive function without sedation. There are several studies that have shown that combined effects of piracetam and ginkgo biloba produced more significant effects than either ginkgo biloba or piracetam alone on cognitive function and working memory.[12] Hence it is very likely that addition of vinpocetine to ginkgo biloba and piracetam would produce better outcomes on cognition.

Part II: Tinnitus and Vertigo

Meniere's syndrome

Meniere's syndrome is a chronic inner-ear disorder characterized by recurrent episodes of spontaneous vertigo and fluctuating unilateral sensorineural hearing loss (SNHL), tinnitus, and aural fullness. When this set of symptoms cannot be attributed to a specifically identified cause, the syndrome is considered idiopathic and then it is referred to as Meniere's disease (MD).[13]

Epidemiology

The worldwide incidence of Meniere's disease is approximately 12 out of every 1,000 people. Perhaps 100,000 patients develop Meniere's disease every year.[14]

The age at the first attack of Meniere's is usually in the third to sixth decade of life. There may be a genetic component to Meniere's, since there is a positive family history in 20% of patients. Patients who are at greater risk include those with a recent viral illness or respiratory infection, those with a history of allergies, smoking, stress, fatigue, or alcohol use, and patients taking aspirin. There does not appear to be a gender preference.[14]

Etiology and pathophysiology

Human temporal bone studies have linked MD symptoms to the accumulation of endolymph within the cochlear duct (scala media) and the sacculus in the inner ear. It is believed that this endolymphatic hydrops (EH) begins with a disturbance of the ionic composition of the scala media. However, current data support the hypothesis that EH is an epiphenomenon associated with a variety of inner-ear disorders, and that genetics and environmental factors contribute to its development. So, food or respiratory allergens, infectious agents, vascular events, or genetic factors could trigger an imbalance in inner-ear homeostasis. Several regulatory factors, such as the innate immune response, the endocrine system, or the autonomic nervous system, may also influence the development of the partial or complete phenotype observed in familial MD. The cumulative effect of one or several triggers and the individual response may explain the clinical heterogeneity observed in MD phenotype (Figure 3).[13]

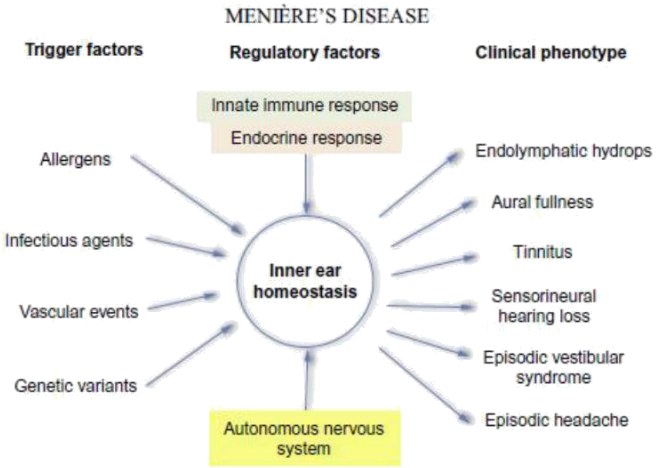

Figure 3: Core hypotheses for Menie`re's disease. Multiple genetic or environmental factors could challenge inner-ear homeostasis and trigger a partial or a complete clinical phenotype, depending on the individual susceptibility, according to several regulatory factors such as the inmate immune response, the endocrine system, and the autonomic nervous system

Clinical manifestations

Numerous factors have been alleged to precipitate an MD attack, including stress, sleep deprivation, some food, allergens, barometric pressure change, and hormonal changes (menses). The occurrence of recurring episodes of spontaneous vertigo is the main feature of MD and it is present in 96.2% of patients. Vertigo is the most disabling symptom, commonly described as spinning, exacerbated by head movements, and accompanied by nausea, vomiting, and sweating. Spells of vertigo last several hours, and when they subside patients complain of unsteadiness for several days. These spells are often preceded by tinnitus, aural fullness, and a decrease in hearing in the affected ear (Figure 6).[13]

Management

The goal of the management of MD is to provide relief during acute attacks of vertigo, to prevent recurrent attacks and to eliminate the progressive damage to hearing and vestibular function in the affected ear (or ears). Although progress has been made on the first two goals, the elimination of the progressive damage to hearing and vestibular function has proved intangible. Most treatments concentrate on relieving the acute symptoms and preventing the recurrence of vertigo attacks.[14]

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Treatment of acute vertigo attacks

Several drugs are used to reduce the asymmetry in neuronal input to the brainstem during vertigo attacks. Drugs that are used to treat motion sickness are useful for acute attacks of

MD91. Centrally acting antihistamines with anticholinergic effects have the dual effect of suppressing the vestibular system while also acting as anti-emetics. Benzodiazepines are also often used for their γaminobutyric acid (GABA) agonist effect.[14]

Preventive treatment

The main goal of preventive treatment is to improve patients' quality of life. This may be achieved by reducing the frequency, duration, and severity of vertigo spells. Preventive treatment includes lifestyle and dietary modifications, pharmacologic therapy, and in some cases surgical procedures. Other treatment options, such as hearing aids, cochlear implants, and the Meniett device, may also provide some benefit.[13]

Lifestyle and dietary modifications

Patients with MD should avoid triggers such as stress, barometric pressure change, fatigue, or sleep deprivation. Alcohol, coffee, and tobacco are traditionally restricted, although the efficacy of these measures has not been demonstrated in randomized controlled trials. The most important dietary recommendation is a high-water intake and a very low sodium diet.[13]

Role of piracetam

Piracetam has been shown to be effective in vertigo of both central and peripheral origin. It is thought to act on vestibular and oculomotor nuclei in the brain stem and thus on the central control of balance enhancing mechanisms of compensation and habituation. A review by Oosterveld of double-blind trials demonstrated that piracetam alleviates vertigo after head injury, vertigo of central origin as, for example, in vertebrobasilar insufficiency and in peripheral vestibular disorders, especially in middle-aged and elderly subjects.[15]

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Role of gingko biloba

Drugs that improve cerebral blood flow are often prescribed in vertigo associated with cerebrovascular disorders.*Ginkgo biloba* extract enhances cerebral and vestibular blood flow by decreasing blood viscosity. It improves neuronal plasticity as well as mitochondrial function and energy metabolism and protects neurons from oxidative damage. Its efficacy

Various randomized controlled trials have proven the efficacy of *Ginkgo biloba* extract vestibular and nonvestibular vertigo

in the treatment of vestibular and nonvestibular vertigo has also been proven by randomized, placebo-controlled trials.[16]

Role of vinpocetine

Vinpocetine has been used successfully for various hearing impairments related to the auditory sensory nerves, as well as for some ear diseases accompanied by vertigo, such as Ménière's disease; it was shown to be superior to the vasodilators used at the time of the study in question.[17] In patients suffering from tuberculosis, vinpocetine helped prevent sensorineural hearing impairment in patients with normal hearing, and it improved hypoacusis in patients who had it.[18]

Vinpocetine has also been used in the treatment of acoustic trauma with subsequent hearing loss and tinnitus. Tinnitus disappeared in 50% of the patients who started vinpocetine within one week of the trauma. For those who started later, 79% had improved hearing, and 66% had a significant decrease in the severity of the tinnitus.[19]

Efficacy of combination therapy for hearing impairment.

There's no cure for tinnitus, but there are treatments that can help quiet the "phantom" sound. For some people, tinnitus is only a small distraction, but for others, it's much more severe. Sometimes the noise from tinnitus may affects the ability to hear real sounds.

Researchers have found that tinnitus treatments tend to be more successful when you combine them.[20]

Hence it is very likely that a combination of piracetam, gingko biloba and vinpocetine would fetch better results with respect to tinnitus and vertigo as compared to the effect of either of the agent when used alone.

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Part III: Pharmacological profile[21]

Summary Product Information

Cogreno Tablet is used for Ear disorders, Improvement of brain function and memory, Brain and its blood vessels activator, Memory problems, Heart problem, non-progressive neuromotor dysfunction and other conditions. Cogreno Tablet may also be used for purposes not listed in this medication guide.

Cogreno Tablet contains Ginkgo Biloba, Piracetam and Vinpocetine as active ingredients.

Cogreno Tablet works by increasing blood supply by dilating blood vessels, reducing blood viscosity, modifying neurotransmitter systems, and reducing oxygen free radicals; providing oxygen in brain and nervous system; increasing blood flow to the brain and heart to protect it from injury.

Qualitative and quantitative composition

Each film coated tablet contains:

- Piracetam BP 800 mg
- Ginkgo biloba extract 60 mg
- Vinpocetine 5mg

Pharmaceutical form

Film coated tablet

Clinical particulars

Therapeutic indications

Piracetam

Studies carried out in the elderly suffering from loss of memory, vertigo, a lack of concentration or of alertness, changes of mood, a deterioration in behavior and personal negligence, demonstrate an improvement in symptoms. These symptoms can also provide an early warning of the onset of pathological ageing such as Alzheimer's Disease, an Alzheimer type of senile dementia, or the dementia produced by multiple cerebral infarcts.

Piracetam is advocated in the treatment of sickle-cell vaso-occlusive crises.

Studies have shown some improvement in children with learning difficulties associated with the written word, particularly with textual understanding which cannot be explained by intellectual backwardness, inadequate education or by the family environment. The

administration of piracetam does not replace other measures also well adapted to correct these learning difficulties, such as remedial teaching

Ginkgo biloba

A traditional herbal medicinal product used to relieve the symptoms of Raynaud's syndrome and tinnitus, based on traditional use only.

Vinpocetine

The primary claim made for vinpocetine is that it decreases fatality and dependency in ischemic stroke. Research results are mixed. Vinpocetine has not been helpful in Alzheimer's disease, but there is some suggestion that it might help some with other dementias and cerebral dysfunction. Very preliminary research additionally suggests that vinpocetine may help protect the eye and ear from injuries caused by trauma (and, in the case of the eye, from infection) and that it might be gastro-protective, ameliorate symptoms of motion sickness and help prevent atherosclerosis.

Posology and method of administration

Cogreno® should be used as prescribed by the physician. The recommendations for the various components are as follows.

Piracetam

Piracetam should be administered orally and may be taken with or without food. The film-coated tablets should be swallowed with liquid.

The total daily dose can range from 30 to 160 mg/kg/day depending on the indication. This is administered twice daily but may also be given in three or four separate doses. When treating severe symptoms, 12 g daily may need to be administered as an intravenous infusion.

Renal impairment

Piracetam is contraindicated in severe renal impairment (renal creatinine clearance of less than 20 ml per minute). The daily dose must be individualized according to renal function.

Hepatic impairment

No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of dose is recommended.

Ginkgo biloba

Adults and the elderly: As prescribed by the physician.

Children and adolescents less than 18 years old: The use in children and adolescents under 18 years of age is not recommended.

Duration of use: If the symptoms worsen or persist for more than 4 weeks a doctor or a qualified healthcare practitioner should be consulted.

Vinpocetine

This is available as an individual supplement and in combination products. Typical doses for supplement use are 5 to 10 milligrams daily with food. Some take up to 20 milligrams daily. Higher doses are not advised. Caution must be exercised before starting to take this medicine. It is vital that doctor should be consulted.

Contraindications

Piracetam is contraindicated in:

- Hypersensitivity to piracetam, other pyrrolidone derivatives or any of the excipients;
- Patients with end-stage renal disease (renal creatinine clearance of less than 20 ml per minute);
- Patients with cerebral hemorrhage;
- Patients suffering from Huntington's Chorea.

Gingko biloba:

Do not use in cases of known hypersensitivity to Ginkgo preparations or to any of the excipients.

Special warnings and precautions for use

Piracetam

Effects on platelet aggregation

Because of piracetam on platelet aggregation, caution is recommended in patients with severe hemorrhage, patients at risk of bleeding such as gastrointestinal ulcer, patients with underlying disorders of hemostasis, patients with history of hemorrhagic CVA, patients undergoing major surgery including dental surgery, and patients using anticoagulants or platelet antiaggregant drugs including low dose aspirin.

Renal insufficiency

Piracetam is eliminated via the kidneys and care should thus be taken in cases of renal insufficiency.

Elderly

For long-term treatment in the elderly, regular evaluation of the creatinine clearance is required to allow dosage adaptation if needed.

Discontinuation

Abrupt discontinuation of treatment should be avoided as this may induce myoclonic or generalized seizures in some myoclonic patients.

Ginkgo biloba

- The use in children and adolescents under 18 years of age is not recommended because data are not sufficient and medical advice should be sought.
- Keep out of the reach and sight of children.
- There are rare case reports of spontaneous bleeding in association with the use of products containing Ginkgo extracts. Although no causal link has been established care should be taken by patients who have a pre-existing bleeding disorder. It is advisable that Ginkgo is discontinued at least 2 weeks prior to surgery or that clotting parameters are assessed prior to surgery.

Vinpocetine

Those with a history of allergic reactions or hypersensitivity reactions during treatment with other vinca alkaloids, such as vinblastine and vincristine, should avoid vinpocetine. Those on warfarin are advised to have their INRs (international normalized ratios) regularly monitored when using vinpocetine supplements (see Interactions). Those with hypotension or orthostatic hypotension should be cautioned that prolonged use of vinpocetine may lead to slight reductions in systolic and diastolic blood pressure.

Interaction with other medicinal products and other forms of interaction

Piracetam

Thyroid hormones

Confusion, irritability and sleep disorder have been reported during concomitant treatment with thyroid extract.

Acenocoumarol

In a published single-blind study on patients with severe recurrent venous thrombosis, piracetam 9.6 g/d did not modify the doses of acenocoumarol necessary to reach INR 2.5 to 3.5, but compared with the effects of acenocoumarol alone, the addition of piracetam 9.6 g/d significantly decreased platelet aggregation, β-thromboglobulin release, levels of fibrinogen and von Willebrand's factors.

Antiepileptic drugs

A 20 g daily dose of piracetam over 4 weeks did not modify the peak and trough serum levels of antiepileptic drugs (carbamazepine, phenytoin, phenobarbitone, valproate) in epileptic patients who were receiving stable doses.

Vinpocetine

Warfarin — Slight changes in prothrombin time have been noted in those adding vinpocetine to warfarin dosing.

Fertility, Pregnancy and lactation

Fertility

There are no relevant data available.

Pregnancy

Piracetam should not be used during pregnancy unless clearly necessary, when benefit exceeds the risks and the clinical condition of the pregnant mother requires treatment with piracetam.

Lactation

Piracetam should not be used during breast-feeding or breast-feeding should be discontinued, while receiving treatment with piracetam.

Vinpocetine

Pregnant women and nursing mothers should avoid vinpocetine supplements.

Undesirable effects

Piracetam

Clinical studies

Double-blind placebo-controlled clinical or pharmaco-clinical trials, of which quantified safety data are available (extracted from the UCB Documentation Data Bank on June 1997), included more than 3000 subjects receiving piracetam, regardless of indication, dosage form, daily dosage or population characteristics.

Frequencies are defined as follows: very common: ≥1/10; common ≥1/100, <1/10; uncommon ≥1/1,000, <1/100; rare ≥1/10,000, <1/1,000; very rare <1/10,000 and not known.

Blood and lymphatic system disorders	
Not known	haemorrhagic disorder
Immune system disorders	
Not known	anaphylactoid reaction, hypersensitivity
Psychiatric disorders	
Common	nervousness
Uncommon	depression
Not known	agitation, anxiety, confusion, hallucination
Nervous system disorders	
Common	hyperkinesia
Uncommon	somnolence
Not known	ataxia, balance impaired, epilepsy aggravated, headache, insomnia
Ear and labyrinth disorders	
Not known	vertigo
Vascular disorders	
Rare	thrombophlebitis (only for injectable form), hypotension (only for injectable form)
Gastrointestinal disorders	
Not known	abdominal pain, abdominal pain upper, diarrhoea, nausea, vomiting
Skin and subcutaneous tissue disorders	
Not known	angio-neurotic oedema, dermatitis, pruritus, urticaria
General disorders and administration site conditions	
Uncommon	asthenia
Rare	pyrexia (only for injectable form), injection site pain (only for injectable form)
Investigations	
Common	weight increased

Ginkgo biloba

- The following adverse reactions have rarely been reported in association with the use of products containing Gingko extract.
- Body as a whole – general disorders
    - Allergy
- Central and peripheral nervous system disorders
    - Headache
- Gastrointestinal system disorders
    - Nausea
    - Vomiting
    - Diarrhea
- Skin and appendages
    - Pruritus
    - Rash
- There have been very rare case reports of Stevens-Johnson syndrome associated with the use of Ginkgo extract.

- There are sporadic case reports of bleeding disorders in patients who have been taking preparations containing Ginkgo extract. The causality in these cases is not established.

Vinpocetine

Reported adverse reactions include nausea, dizziness, insomnia, drowsiness, dry mouth, transient hypotension, transient tachycardia, pressure-type headache and facial flushing. Slight reductions in both systolic and diastolic blood pressure with prolonged use of vinpocetine have been reported, as well as slight reductions in blood glucose.

Pharmacological properties

Pharmacodynamic properties

Piracetam

Mechanism of Action

Available data suggest that piracetam basic mechanism of action is neither cell- nor organ-specific. Piracetam binds physically in a dose-dependent manner to the polar head of phospholipids membrane models, inducing the restoration of the membrane lamellar structure characterized by the formation of mobile drug-phospholipid complexes. This probably accounts for an improved membrane stability, allowing the membrane and transmembrane proteins to maintain or recover the three-dimensional structure or folding essential to exert their function. Piracetam has neuronal and vascular effects.

At the neuronal level, piracetam exerts its membrane activity in various ways. In animals, piracetam enhances a variety of types of neurotransmission, primarily through postsynaptic modulation of receptor density and activity. In both animals and man, the functions involved in cognitive processes such as learning, memory, attention and consciousness were enhanced, in the normal subject as well as in deficiency states, without the development of sedative or psychostimulant effects. Piracetam protects and restores cognitive abilities in animals and man after various cerebral insults such as hypoxia, intoxications and electroconvulsive therapy. It protects against hypoxia-induced changes in brain function and performance as assessed by electroencephalograph (EEG) and psychometric evaluations.

Ginkgo biloba

No information is available

Vinpocetine

Vinpocetine has several possible actions, including increasing cerebral blood flow and metabolism, anticonvulsant, cognition enhancement, neuroprotection and antioxidant. Vincamine, the parent compound of vinpocetine, is believed to be a cerebral vasodilator

Mechanism of action

Several mechanisms have been proposed for the possible actions of vinpocetine

Vinpocetine has been reported to have calcium-channel blocking activity, as well as voltage-gated sodium channel blocking activity. It has also been reported to inhibit the acetylcholine release evoked by excitatory amino acids and to protect neurons against excitotoxicity. In addition, vinpocetine has been shown to inhibit a cyclic GMP phosphodiesterase, and it is speculated that this inhibition enhances cyclic GMP levels in the vascular smooth muscle, leading to reduced resistance of cerebral vessels and increase of cerebral flow. In some studies, vinpocetine has demonstrated antioxidant activity equivalent to that of vitamin E.

Pharmacokinetic properties

Piracetam

The pharmacokinetic profile of piracetam is linear and time-independent with low inter-subject variability over a large range of doses. This is consistent with the high permeability, high solubility and minimal metabolism of piracetam. Plasma half-life of piracetam is 5 hours. It is similar in adult volunteers and in patients. It is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment. Steady state plasma concentrations are achieved within 3 days of dosing.

Absorption

Piracetam is rapidly and extensively absorbed following oral administration. In fasted subjects, the peak plasma concentrations are achieved 1 hour after dosing. The absolute bioavailability of piracetam oral formulations is close to 100%. Food does not affect the extent of absorption of piracetam, but it decreases Cmax by 17% and increases Tmax from 1 to 1.5 hours. Peak concentrations are typically 84 µg/ml and 115 µg/ml following a single oral dose of 3.2 g and repeat dose of 3.2 g t.i.d. respectively.

Distribution

Piracetam is not bound to plasma proteins and its volume of distribution is approximately 0.6 l/kg. Piracetam crosses the blood brain barrier as it has been measured in cerebrospinal fluid following intravenous administration. In cerebrospinal fluid, the Tmax was achieved about 5 hours post-dose and the half-life was about 8.5 hours. In animals, piracetam highest

concentrations in the brain were in the cerebral cortex (frontal, parietal and occipital lobes), in the cerebellar cortex and in the basal ganglia. Piracetam diffuses to all tissues except adipose tissues, crosses placental barrier and penetrates the membranes of isolated red blood cells.

Metabolism

Piracetam is not known to be metabolized in the human body. This lack of metabolism is supported by the lengthy plasma half-life in anuric patients and the high recovery of parent compound in urine.

Elimination

The plasma half-life of piracetam in adults is about 5 hours following either intravenous or oral administration. The apparent total body clearance is 80-90 ml/min. The major route of excretion is via urine, accounting for 80 to 100% of the dose. Piracetam is excreted by glomerular filtration.

Special patient populations

Children: No formal pharmacokinetic study has been conducted in children.

Elderly: In the elderly, the half-life of piracetam is increased and the increase is related to the decrease in renal function in this population.

Renal impairment

Piracetam clearance is correlated to creatinine clearance. It is therefore recommended to adjust the daily dose of piracetam based on creatinine clearance in patients with renal impairment.

Hepatic impairment

The influence of hepatic impairment on the pharmacokinetics of piracetam has not been evaluated. Because 80 to 100% of the dose is excreted in the urine as unchanged drug, hepatic impairment solely would not be expected to have a significant effect on piracetam elimination.

Ginkgo biloba

No information is available.

Vinpocetine

Vinpocetine is absorbed from the small intestine, from whence it is transported to the liver via the portal circulation. From the liver via the systemic circulation, it is distributed to various tissues in the body, including the brain. Absorption of vinpocetine is

significantly higher when given with food and can be up to about 60% of an ingested dose. On an empty stomach, absorption of an ingested dose can be as low as 7%. Peak plasma levels are obtained one to one and a half hours after ingestion. Extensive metabolism to the inactive apovincaminic acid occurs in the liver. Only small amounts of unmetabolized vinpocetine are excreted in the urine, the major route of excretion of apovincaminic acid. Most of a dose is excreted within 24 hours as this metabolite. The elimination half-life of vinpocetine following ingestion is one to two hours.

Preclinical safety data

Piracetam

Single doses of piracetam yielded LD50 values at 26 g/kg in mice but LD50 values were not reached in rats. In dogs, clinical signs after acute oral dosing were mild and lethality was not observed at the maximum tested dose of 10 g/kg.

Repeated oral treatment for up to 1 year in dogs (10 g/kg) and 6 months in rats (2 g/kg) was very well tolerated: no target organ toxicity or signs of (irreversible) toxicity were clearly demonstrated. Safe dose levels represent a multiple of the maximum intended human daily dose of 0.4 g/kg.

In terms of exposure (Cmax) safe levels obtained in the rat and the dog represent respectively 8-fold and 50-fold of the maximum human therapeutic level. AUC levels obtained in the same animals were a multiple of the human AUC level at the maximum intended daily dose.

The only change which might eventually be attributed to chronic treatment in male, but not in female, rats was an increase of the incidence over control animals of progressive glomerulo-nephrosis at the dose of 2.4 g/k/day given for 112 weeks.

Although piracetam crosses the placenta into the fetal circulation, no teratogenic effects were observed at dose levels up to 4.8 g/kg/day (mice, rats) and 2.7 g/kg/day (rabbits). Furthermore, the compound affects neither fertility nor the peri- or postnatal development of the pregnancy at doses up to 2.7 g/kg/day.

Piracetam was found to be devoid of any mutagenic or clastogenic activity and does not represent any genotoxic or carcinogenic risk to man.

Ginkgo biloba

The preclinical toxicology data available are limited. An in vitro study has shown the aqueous ethanolic Ginkgo extract used in this product to be non-mutagenic in the Salmonella

typhimurium reverse mutation assay up to the dose of 5,000 µg/plate. Tests on reproductive toxicity and carcinogenicity have not been performed

Vinpocetin

No data is available for ***vinpocetine***

Pharmaceutical particulars

List of excipients

Titanium dioxide

Incompatibilities

Not known

Shelf life

24 months

Special precautions for storage

Store in a cool dry place, protect from light

Part IV: Clinical profile

Piracetam

Piracetam belongs to a class of nootropic compounds which are known to modulate cerebral functions. It aims to increase cerebral blood flow, enhance oxygen extraction, restore membrane fluidity, and modulate neurotransmission. Piracetam was reported to increase cerebral blood flow and glucose metabolism in both infarcted and penumbral tissues, and its neuroprotective efficacy was confirmed in a meta-analysis of experimental stroke using rat models.[22]

Clinical Efficacy of Piracetam in Cognitive Impairment[23]

Piracetam has been promoted in over 120 countries globally, for the symptomatic treatment of psycho-organic syndromes in dosages of up to 4.8 g per day, and for the treatment of cerebrovascular accidents and its sequelae, aphasia, in dosages up to12 g per day. Furthermore, piracetam is approved for cortical myoclonus in dosages of up to 24 g per day. Piracetam directly enhances, in both animals and man, the functions involved in cognitive processes such as learning, memory, attention and consciousness, without the development of sedative or psychostimulant effects.

Waegemans et al performed a meta-analysis of clinical studies that have been reported between 1972 and the first half of 2001 to evaluate the efficacy of piracetam.

Methods

The study protocol is described in Figure 4.

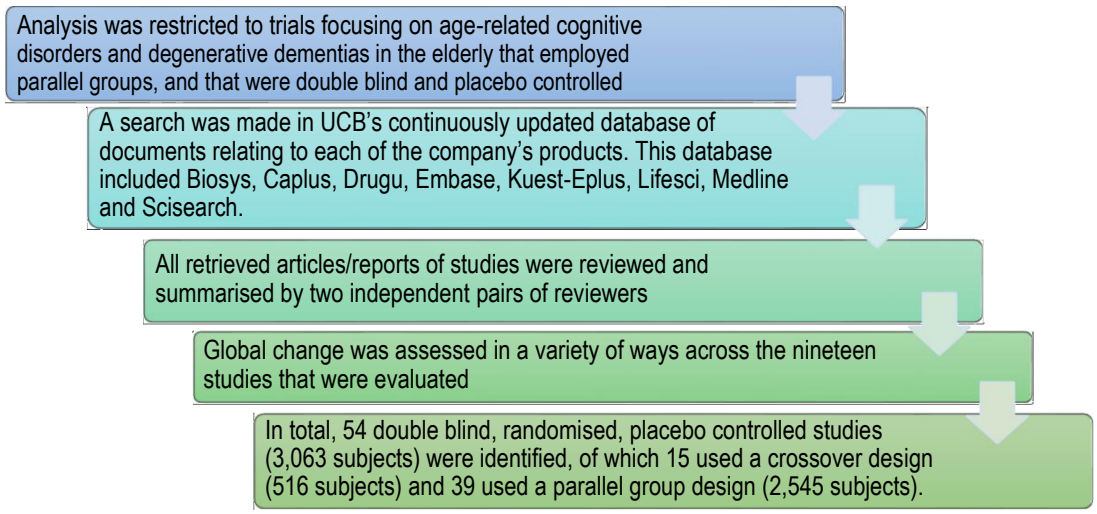

Figure 4: The study protocol

Results

The results of the meta-analysis demonstrate a difference between those individuals treated with piracetam and those given placebo, both as significant odds ratio and as a favorable number needed to treat. The global change results for each of the nineteen studies included in the meta-analysis are summarized in Figure 5.

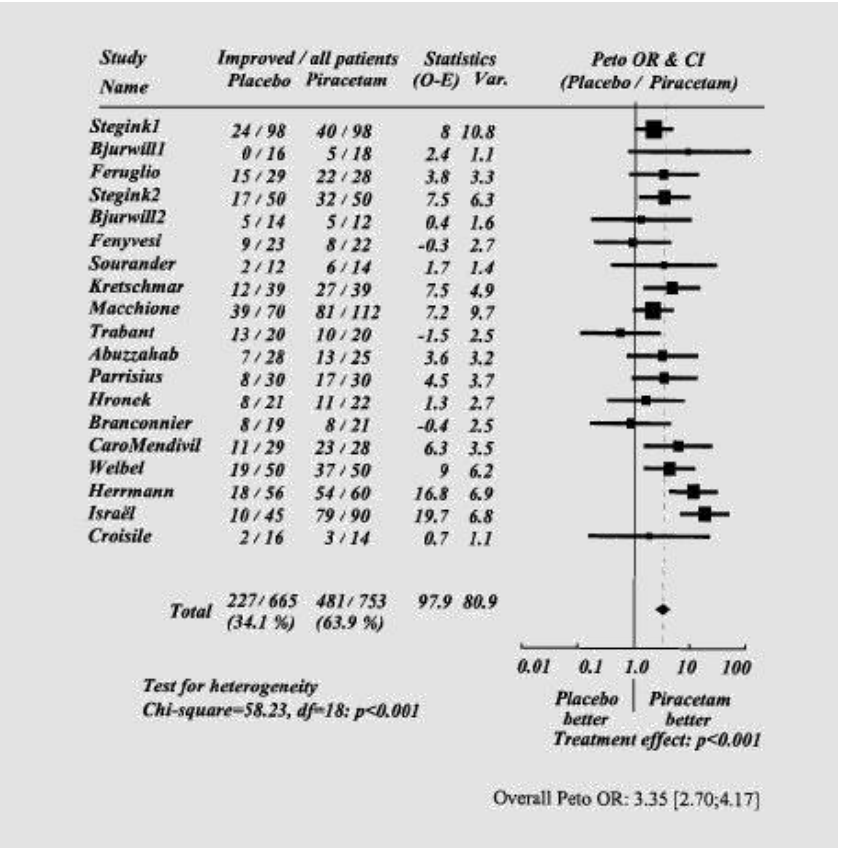

Figure 5: Global change results for each of the 19 studies included in the meta-analysis of piracetam in dementia or cognitive impairment (fixed effects model; population of observed cases).

Conclusion

These results provide compelling evidence for the global clinical efficacy of piracetam in a diverse group of older subjects with cognitive impairment. To confirm the findings of this meta-analysis, prospective, double blind, placebo-controlled studies, using modern diagnostic and efficacy measures, should be conducted

These results provide compelling evidence for the global clinical efficacy of piracetam in a diverse group of older subjects with cognitive impairment

Piracetam for Aphasia in Post-stroke Patients[24]

Aphasia is a common symptom in post-stroke patients. Piracetam is a commonly used nootropic agent that promises various benefits to brain function, including language improvement. Zhang et al performed a systematic review and meta-analysis to assess whether piracetam facilitates the rehabilitation of language performance in post-stroke patients.

Methods

The study protocol is described in Figure 6.

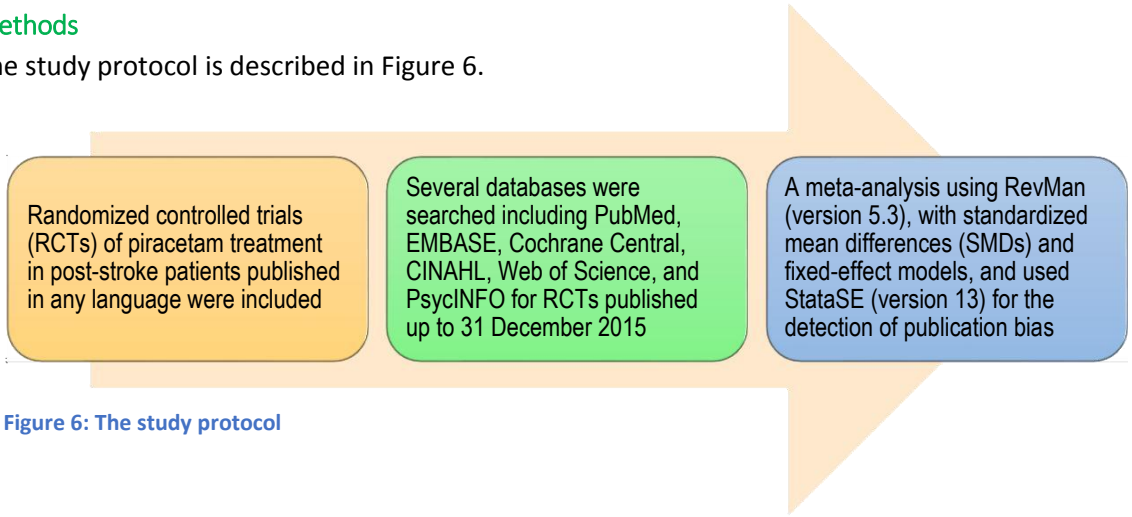

Figure 6: The study protocol

Results

- This systematic review and meta-analysis indicated that of piracetam may have some efficacy on the overall severity of language impairment.
- Subtest performance detected a task-specific effect that piracetam improved written language performance significantly.
- Subgroup analyses showed a time-related dissociation of the nootropic effect between short and long-term assessments, and implied only short-term advantages in overall and written language performance (Figure 7).

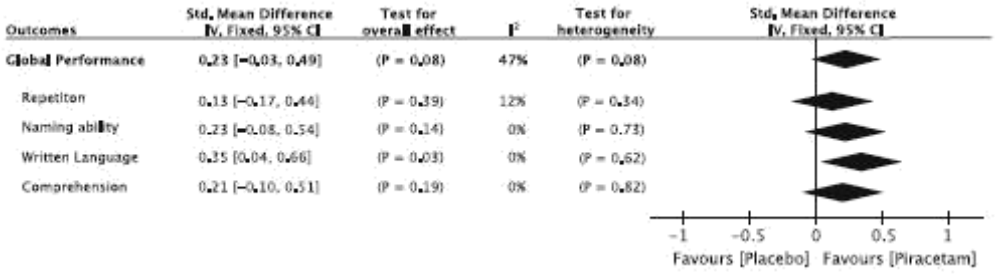

Figure 7: Summary forest plot depicting the efficiency of piracetam in global assessment and subtests at the end of trials. CI confidence interval, IV inverse variance, Std standardized

Conclusion

Our systematic review and meta-analysis demonstrates piracetam benefits written language ability at the end of trials, which could be a potential target for further research. The effect tends to emerge within a short period and decline in longer therapy, with regards to the overall severity of aphasia and written language ability. This time-related dissociation of the nootropic effect is critical for verifying its pharmacological efficacy and is vital to understand for future piracetam therapy.

Piracetam benefits written language ability at the end of trials, which could be a potential target for further research

The Effectiveness of Piracetam in Vertigo[25]

The nootropic drug piracetam has been found to be beneficial in vertigo of both central and peripheral origin. Piracetam improves higher cerebral integrative functions but does not possess sedative or psychostimulant properties. Piracetam is thought to act on the vestibular and oculomotor nuclei in the brain stem and thus on the central mechanism for the control of balance. This is probably the basis for its effects in patients with both central and peripheral vertigo in whom it enhances the processes of adaptation and compensation.

Clinical Trials with Piracetam

Three studies in patients with vertigo and other symptoms persisting for at least two months after head injury showed significant benefit for piracetam relative to placebo.

- Aantaa and Meurman demonstrated that piracetam caused significant improvement in vertigo and spontaneous and positional nystagmus in patients with post-concussional vertigo and headache (Figure 8)

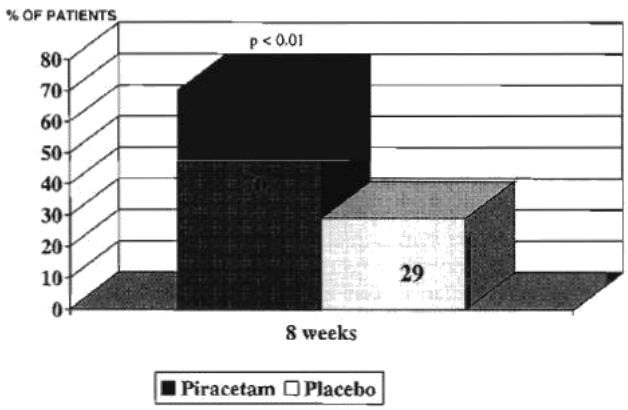

Figure 8: Vertigo after head injury. Percentage of patients with disappearance of vertigo after B weeks' treatment with piracetam and placebo

- Similar findings were reported by Hakltareinen and Hakamies (1978) who in addition found significant improvement in headache and a decrease in other symptoms (Figure 9).

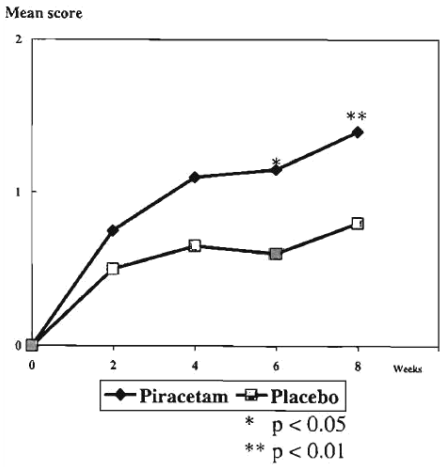

Figure 9: Vertigo after head injury. Evolution during 8 weeks' treatment with piracetam and placebo (Hakkarainen and Hakamies, 1978

- Haguenauer et al studied two comparable groups of patients with vertigo of labyrinthine or rerrolabyrinrhine origin and recorded marked and significant improvement in the piracetam group relative to placebo in the frequency and severity of episodes of vertigo, in tinnitus and in social and professional functioning (Figure 10).

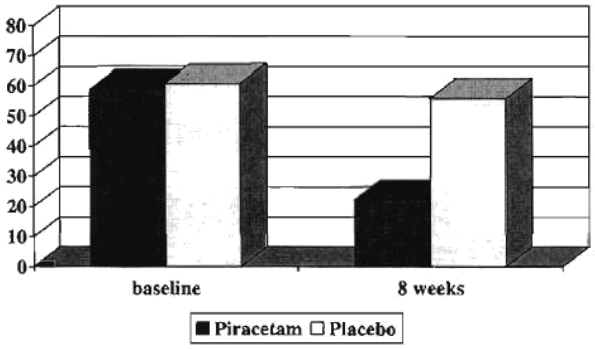

Figure 10: Vertigo of various origins (central and peripheral). Severity assessed by investigator after 8 weeks' treatment with piracetam and placebo

In a multicenter study in 143 middle-aged and elderly patients (mean age 61 years) with chronic or recurrent vertigo of either central or peripheral origin, Rosenhall et al. (1996) found significant improvement after piracetam: episodes of vertigo were significantly less frequent but not less severe on piracetam than placebo and the duration of incapacity was less (Figure 11). Malaise between episodes and imbalance improved significantly more on piracetam (Figure 12).

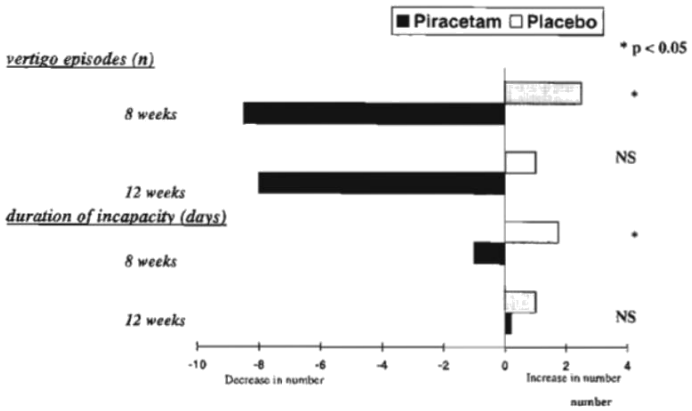

Figure 11: Vertigo of various origins (central and peripheral). After 8 weeks' treatment with piracetam and placebo the frequency of episodes of vertigo and the duration of incapacity were both significantly less (P < 0.05) after piracetam than placebo. At 12 weeks, 4 weeks after withdrawal of treatment, the difference between treatment groups was no longer significant (Rosenhall et al. 1996).

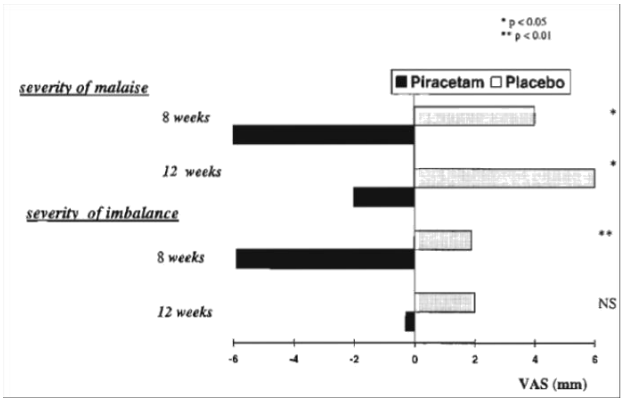

Figure 12: Vertigo of various origins (central and peripheral). Severity of malaise and imbalance between episodes of vertigo assessed by visual analog scale (VAS) after 8 weeks' treatment with piracetam and placebo and at 12 weeks, 4 weeks after withdrawal of treatment. Both symptoms improved significantly after 8 weeks (malaise P<0.05. imbalance P<0.01) while at 12 weeks significant improvement had occurred only in malaise (P < 0.05) (Rosenhall et al., 1996).

Conclusion

Piracetam. in a dose of 2.4-4.8 g/day may diminish the frequency of exacerbations in patients with recurrent and chronic vertigo. It is suitable for long-term use. It has a benign adverse effect profile and withdrawal from treatment because of side effects is unusual.

Efficacy of Piracetam in Tinnitus and Hearing loss

Piracetam, the most common of the nootropic drugs, is a cyclic derivative of gamma-aminobutyric acid (GABA). It influences neuronal and vascular function, improves memory and brain performance and acts on cognitive function without causing sedation or stimulation. Piracetam also possess antihypoxic effect. It increases blood flow and oxygen consumption in parts of brain. The peripheral vascular effect of piractem has been indicated for its use for sudden deafness and tinnitus. The minimum total duration of therapy is 4-6 weeks. Nootropic drugs can be recommended for the treatment of acute

and chronic tinnitus. Table 2 summarizes the efficacy studies of piractem in tinnitus and hearing loss.[26]

Table 2: Efficacy studies of Piracetam in Tinnitus and hearing loss

Author	Study details	Outcome
Gutmann and Mees (1995).[27]	– In a prospective randomized clinical study, the therapeutic efficacy of piracetam/HAES 6% was compared with that of naftidrofuryl/HAES 6% in 39 patients with tinnitus and sudden hearing loss. – The parameters evaluated were hearing improvement and the reduction in intensity of tinnitus	– Improvement in hearing was 15 dB (piracetam) versus 18.5 dB (naftidrofuryl). – The improvement in tinnitus amounted 27 dB (piracetam) and 19.9 dB (naftidrofuryl). – **Piracetam, which improves rheology and has a positive effect on metabolism, would appear of interest for the treatment of acute tinnitus**.
García Callejo, et al (2000).[28]	– The usefulness of the rheoactive agent piracetam and prednisolone was compared with steroid/ vasodilator therapy, to determine if blood viscosity disorders affect the clinical course of idiopathic sudden deafness	– The piracetam group (n=17) showed clinical improvement in 82.3% and a mean hearing gain in 54.1%, compared with 68.7% and 49.3%, respectively, for the group without piracetam (n = 6). – On the seventh day after onset, all the viscosity parameters had returned to normal in the piracetam group, but the non-piracetam group still showed no improvement in whole blood viscosity and erythrocyte filterability.\ – **Piracetam seemed to be effective in this sensorineural deafness, probably because of its effect on the viscoelastic properties of blood.**
Gersdorff and Franceschi (1986)[29]	– The authors report ten cases of sudden deafness atreated by piracetam.	– In eight cases there was a complete recovery, in one case there was a partial recovery and in one it was a failure. – The researchers observed a rise in the compound action potential of the electrocochleography measured after 30 minutes of the infusion in comparison with that performed 30 minutes before the infusion. – **Piracetam caused a rapid recovery of hearing loss and did not cause any side effects.**

A Comparative Study to Determine the Efficacy of Piracetam over Carbamazepine in the Treatment of Idiopathic Tinnitus[30]

Simha and Ravishankar aimed to determine whether Piracetam or Carbamazepine is efficient in treating cases of idiopathic tinnitus.

Methods

- The study was conducted on patients of age 20 yrs and above of either sex who presented with chronic tinnitus.
- Patients were randomized into 2 study groups and 1 control group.
    - The first study group comprised of 20 patients and were administered
    - The second study group comprised of 20 patients and were administered Carbamazepine 200mg thrice daily for 3 months.
    - The control group comprised of 20 patients and were given B-complex capsules once daily
- Patients were followed up for 3 months and were assessed with Tinnitus Handicap Inventory (THI) Questionnaire and Pure Tone Audiometry both pre and post treatment to evaluate which drug is better.

Results

- Percentage change in THI score between pre and post treatment with Carbamazepine was as following: mild+10.3, moderate-8.7, severe-8.7.
- Percentage change in THI score between pre and post treatment with Piracetam was as following: mild+63.3, moderate-33.3, severe-20.0.
- Percentage change in THI score between pre and post treatment with placebo was as following: mild+4.3, moderate-4.3, severe0.0.
- Pure Tone Audiometry test showed statistically significant improvement in hearing in those patients treated with Piracetam with a p value 0.007.

Conclusion

Thus, in our study we concluded that use of Piracetam helps in reducing tinnitus and improve sensorineural hearing loss in patients with tinnitus and the treatment should continue if tinnitus persists. Carbamazepine was not found to be effective in reducing tinnitus. Thus, Piracetam is effective as a modality of treatment in suppressing tinnitus.

Piracetam helps in reducing tinnitus and improve sensorineural hearing loss in patients with tinnitus and the treatment should continue as long as tinnitus persists

Summary of studies on Piracetam for Cognitive impairment, vertigo, tinnitus and sensorineural hearing loss.

The efficacy studies on piracetam are summarized in Table 3

Table 3: Summary of studies on Piracetam in cognitive impairment and vertigo

Author	Outcome
Waegemans et al	There is compelling evidence for the global clinical efficacy of piracetam in a diverse group of older subjects with cognitive impairment
Zhang et al	Piracetam benefits written language ability at the end of trials, which could be a potential target for further research
Aantaa and Meurman	Piracetam caused significant improvement in vertigo and spontaneous and positional nystagmus in patients with post-concussional vertigo and headache
Haguenauer et al	As compared to placebo, piracetam caused a significant improvement in the frequency and severity of episodes of vertigo, in tinnitus and in social and professional functioning
Rosenhall et al	There was significant improvement after piracetam: episodes of vertigo were significantly less frequent, and the duration of incapacity was less
Gutmann and Mees.	Piracetam, which improves rheology and has a positive effect on metabolism, would appear of interest for the treatment of acute tinnitus.
García Callejo, et al	Piracetam seemed to be effective in this sensorineural deafness, probably because of its effect on the viscoelastic properties of blood.
Gersdorff and Franceschi	Piracetam caused a rapid recovery of hearing loss and did not cause any side effects.
Simha and Ravishankar	Piracetam helps in reducing tinnitus and improve sensorineural hearing loss in patients with tinnitus and the treatment should continue as long as tinnitus persists

Gingko biloba

Ginkgo biloba extract is beneficial in the treatment of dementia and other neurodegenerative diseases. Most commercially available preparations are standardized to two active ingredients: flavone glycosides and terpenoids. The flavonoid constituent is a strong antioxidant and is believed to have a general neuroprotective benefit. The terpenoid fraction interferes with platelets and helps individuals recover following a stroke by decreasing the risk of blood clots in the brain and reducing nerve cell death associated with stroke. Constituents of Ginkgo may also inhibit neurotoxicity and nerve cell death caused by nitric oxide.[31] The efficacy studies on gingko biloba in cognitive impairment as well as vertigo and tinnitus are summarized below.

Efficacy and Adverse Effects of Ginkgo Biloba for Cognitive Impairment and Dementia[32]

Research into Ginkgo biloba has been ongoing for many years, while the benefit and adverse effects of Ginkgo biloba extract EGb761 for cognitive impairment and dementia has been discussed controversially. Tan et al discussed new evidence on the clinical and adverse effects of standardized Ginkgo biloba extract EGb761 for cognitive impairment and dementia.

Methods

The study protocol is described in Figure 13

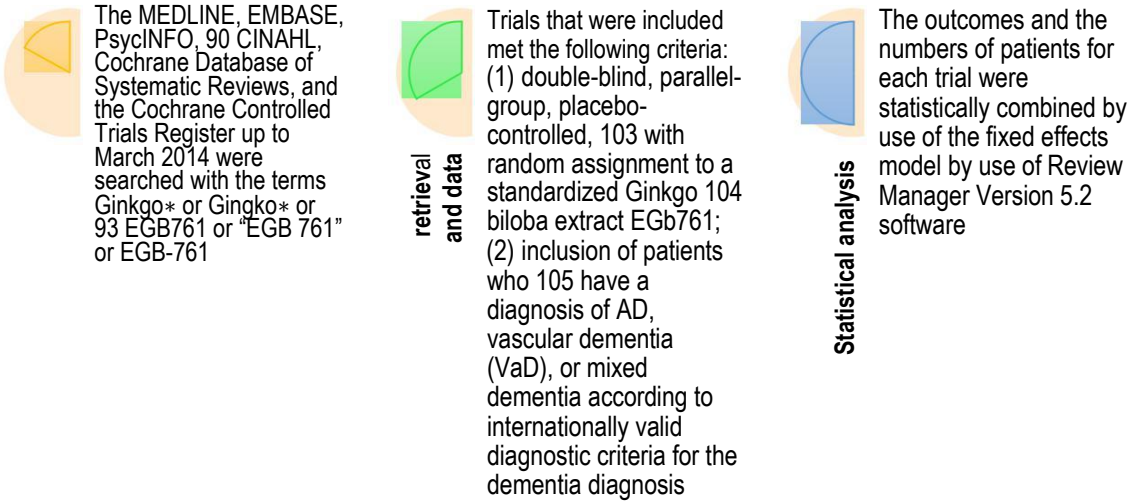

Figure 13: The study protocol

Results

- Trials were of 22–26 weeks duration and included 2,561 patients in total.
- In the meta-analysis, the weighted mean differences in change scores for cognition were in favor of EGb761 compared to placebo (−2.86, 95%CI −3.18; −2.54); the standardized mean differences in change scores for activities in daily living (ADLs) were also in favor of EGb761 compared to placebo (−0.36, 95%CI −0.44; −0.28); Peto OR showed a statistically significant difference from placebo for Clinicians' Global Impression of Change (CGIC) scale (1.88, 95%CI 1.54; 2.29) (Figure 14).
- All these benefits are mainly associated with EGb761 at a dose of 240 mg/day.
- For subgroup analysis in patients with neuropsychiatric symptoms, 240 mg/day EGb761 improved cognitive function, ADLs, CGIC, and neuropsychiatric symptoms with statistical superiority than for the whole group. For the Alzheimer's disease subgroup, the main

outcomes were almost the same as the whole group of patients with no statistical superiority.

- Finally, safety data revealed no important safety concerns with EGb761.

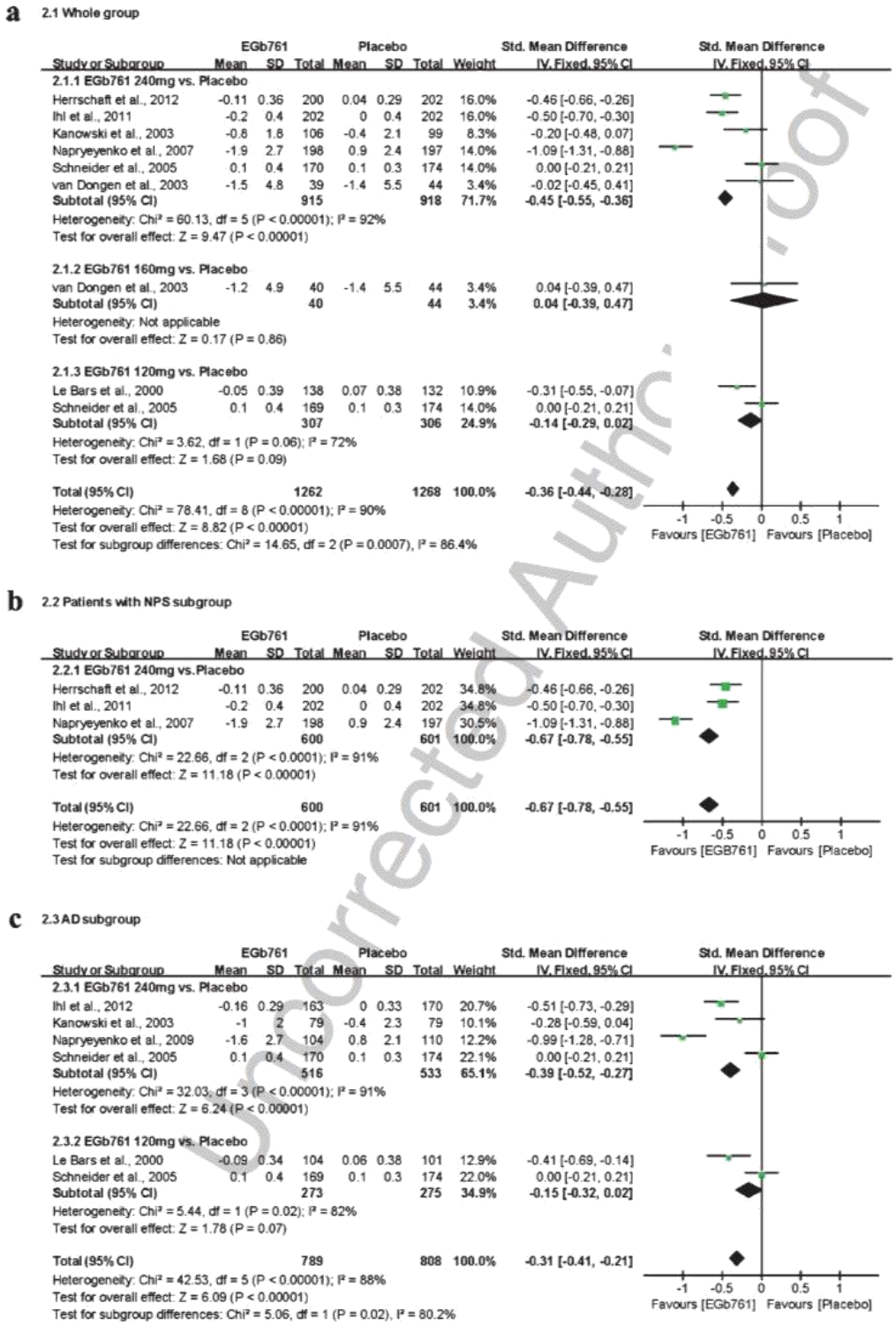

Figure 14: Comparison EGb761 versus placebo, Outcome of Activities of Daily Living (change from baseline after treatment of 22–26 weeks) in whole group (a), in patients with neuropsychiatric symptoms subgroup (b), and in Alzheimer's disease subgroup (c).

Conclusion

EGb761 at 240 mg/day can stabilize or slow decline in cognition, function, behavior, and global change at 22–26 weeks in cognitive impairment and dementia, especially for patients with neuropsychiatric symptoms.

Ginkgo Biloba for Mild Cognitive Impairment and Alzheimer's Disease[33]

Yang et al aimed to explore the effectiveness and safety of Ginkgo biloba in treating mild cognitive impairment and Alzheimer's disease.

Methods

The researchers carried out electronic search from PubMed, Cochrane Library for randomized clinical trials on Ginkgo biloba in treating mild cognitive impairment or Alzheimer's disease. Meta-analyses were performed by RevMan 5.2 software.

Results

- A total of 21 trials with 2608 patients met the inclusion criteria.
- The general methodological quality of included trials was moderate to poor.
- Compared with conventional medicine alone, Ginkgo biboba in combination with conventional medicine was superior in improving Mini-Mental State Examination (MMSE) scores at 24 weeks for patients with Alzheimer's disease (MD 2.39, 95% CI 1.28 to 3.50, P<0.0001) and mild cognitive impairment (MD 1.90, 95% CI 1.41 to 2.39, P<0.00001), and Activity of Daily Living (ADL) scores at 24 weeks for Alzheimer's disease (MD -3.72, 95% CI -5.68 to -1.76, P=0.0002).
- Adverse events were mild.

Conclusion

Ginkgo biloba is potentially effective in improving cognitive function, activities of daily living, and global clinical assessment for patients with mild cognitive impairment or Alzheimer's disease.

A double-blind, placebo-controlled, randomized trial of Ginkgo biloba extract EGb 7611 in a sample of cognitively intact older adults: neuropsychological findings[34]

There appears to be an absence of large-scaled clinical trials that have examined the efficacy of Ginkgo biloba extract on the neuropsychological functioning of cognitively intact older adults. The importance of such clinical research appears paramount in light of the plethora of products containing Ginkgo biloba that are currently being widely marketed to predominantly cognitively intact adults with claims of enhanced cognitive performances. Mix et al aimed to conduct the first known, large-scaled clinical trial of the efficacy of Ginkgo biloba extract (EGb 7611) on the neuropsychological functioning of cognitively intact older adults.

Methods

The study protocol is described in Figure 15.

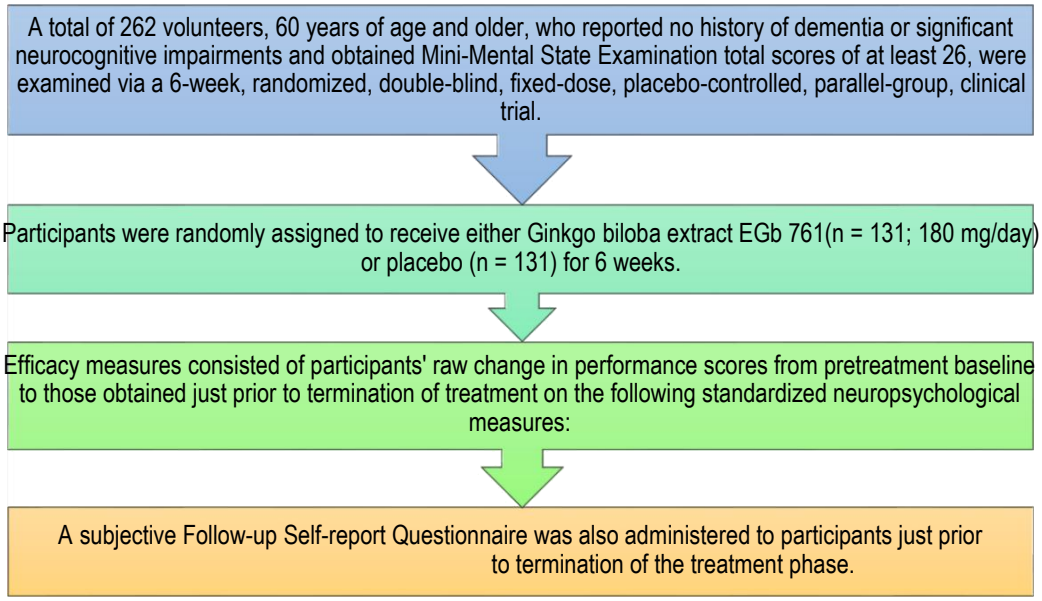

Figure 15: The study protocol

Results

- Cognitively intact participants who received 180 mg of EGb 761 daily for 6 weeks exhibited significantly more improvement on SRT tasks involving delayed (30 min) free

recall ($p < 0.04$) and recognition ($p < 0.01$) of non-contextual, auditory-verbal material, compared with the placebo controls.

- The EGb 761 group also demonstrated significantly greater improvement on the WMS-III FII subtest assessing delayed (30 min) recognition ($p < 0.025$) of visual material (i.e. human faces), compared with the placebo group (Table).
- An examination of the participants' subjective ratings of their overall abilities to remember by treatment end on the Follow-up Self-report Questionnaire also revealed that significantly more ($p = 0.05$) older adults in the EGb 761 group rated their overall abilities to remember by treatment end as 'improved' compared with the placebo controls (Table 4).

Table 2. Neuropsychological test change in performance scores: means and standard deviations

	Ginkgo		Placebo	
Test/variable	Mean	SD	Mean	SD
Selective Reminding Test (raw scores)				
Immediate free recall	15.27	12.11	14.18	12.26
Long-term storage	19.97	19.51	18.44	18.97
Short-term recall	−6.73	9.16	−6.07	8.71
Long-term retrieval	22.00	19.22	20.25	18.87
Consistent long-term retrieval	24.82	26.40	24.26	27.15
Random long-term retrieval	−2.81	17.83	−4.01	18.38
Cued recall	1.04	1.67	1.32	1.64
Delayed free recall	1.69	1.79	1.13	1.95[a]
Delayed recognition	0.43	0.88	0.16	0.77[a]
Wechsler Adult Intelligence Scale-III (raw scores)				
Block design	2.29	5.61	1.88	5.19
Digit symbol	4.53	7.36	3.52	5.61
Wechsler Memory Scale-III (raw scores)				
Faces I	3.72	4.08	3.61	3.96
Faces II	3.48	4.19	2.25	3.82[a]

Conclusion

Overall, the results from both objective, standardized, neuropsychological tests and a subjective, follow-up self-report questionnaire provided complementary evidence of the potential efficacy of Ginkgo biloba EGb 7611 in enhancing certain neuropsychological/memory processes of cognitively intact older adults, 60 years of age and over.

Treatment of Vertigo: A Randomized, Double-Blind Trial Comparing Efficacy and Safety of Ginkgo Biloba Extract EGb 761 and Betahistine[35]

Ginkgo biloba extract EGb 761 improves cerebral and vestibular blood flow by decreasing blood viscosity. It improves neuronal plasticity as well as mitochondrial function and energy metabolism and protects neurons from oxidative damage. Its efficacy in the treatment of vestibular and nonvestibular vertigo has also been proven by randomized, placebo-controlled trials.

Sokolova et al aimed to compare efficacy and safety of EGb 761 to that of the most frequently prescribed antivertigo agent, betahistine, in patients with vertiginous syndromes.

Methods

The study protocol is described in Figure 16.

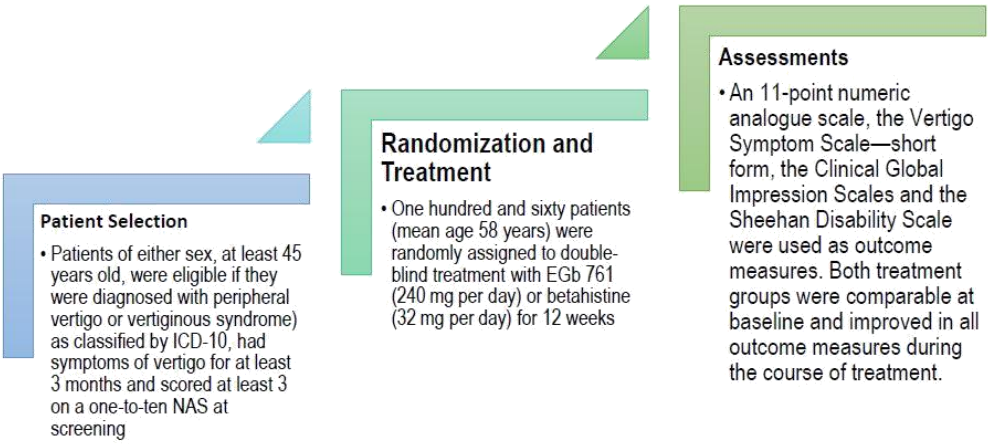

Figure 16: The study protocol

Results

- Numerically, improvements of patients receiving EGb 761 were slightly more pronounced on all scales.
- Clinical global impression was rated “very much improved” or “much improved” in 79% of patients treated with EGb 761 and in 70% receiving betahistine (Figure 17).
- With 27 adverse events in 19 patients, EGb 761 showed better tolerability than betahistine with 39 adverse events in 31 patients

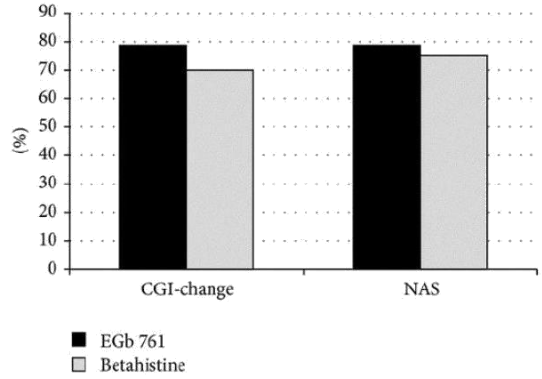

Figure 17: Response rates, defined as clinician's global impression (CGI) rated "much improved" or "very much improved" or patient's rating of NAS improvement at least 50%.

Conclusion

This study provides evidence that the effect of *Ginkgo biloba* extract EGb761 is slightly more pronounced than the world's most frequently prescribed antivertiginous agent, betahistine, in the treatment of unspecified vertiginous syndromes

Modulation Effects of Piracetam and Ginkgo Biloba on the Cognitive and Working Memory Functions[36]

Alkuraishy et al aimed to determine the advancement outcomes of ginkgo and or piracetam on cognitive, psychomotor performances and working memory functions in normal young male's healthy persons and to confirming the modulation effects.

Methods

The study protocol is described in Figure 18.

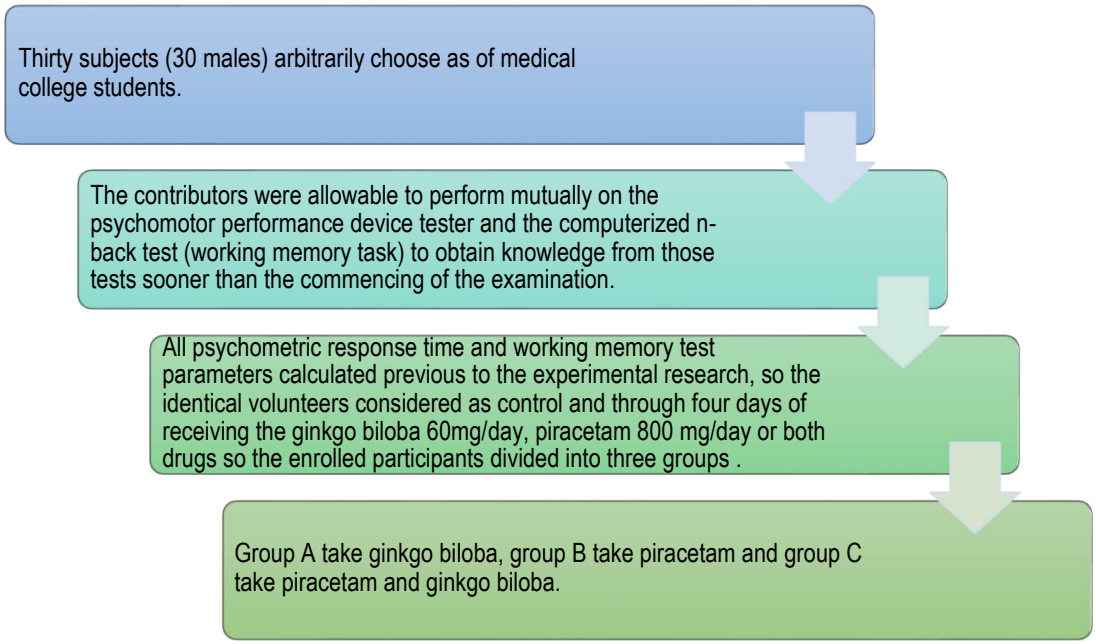

Figure 18: The study protocol

Results

- Piracetam significantly improve cognitive and working memory at all levels P<0.05 while it showed insignificant effects on psychometric reaction time parameters except it ameliorate the total reaction time (TRT) P <0.05.
- The differential effects of ginkgo biloba showed significant effects on psychometric reaction time and cognitive central Integrity P<0.05 and insignificant effects on working memory accuracy except at level I-Back where it produced significant effects P<0.05.
- Combined effects of gingko biloba and piracetam on psychomotor performances, cognitive function and working memory produced significant effects P <0.05 (Table 5).

Table 5: Combined effects of ginkgo biloba and piracetam on psychomotor performances, cognitive function and working memory produced significant effects p<0.05

Psychometric Reaction time				Cognitive central Integrity	Working memory accuracy(%)			
Variables	TRT (ms)	RRT (ms)	MRT (ms)	AFFF	DFFF	I-Back	II-Back	III-Back
Before	525.71 ± 72.5	477.8 ± 15.4	47.91 ± 57.1	40.32 ± 0.007	41.43 ± 0.151	81.4 ± 7.3	82.6 ± 16.3	64.6 ± 12.3

After	321.34 ± 32.3	289.7 ± 22.9	31.64 ± 9.4	49.55 ± 1.407	30.434 ± 0.162	99.8 ± 11.2	95.5 ± 12.5	86.7 ± 14.3
p-value	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

Dual differential combined effects of piracetam and ginkgo biloba on psychomotor, cognitive and working memory performance functions. TRT=total reaction time, RT=recognition reaction time, MRT=movement reaction time, AFFF=ascending flicker fusion frequency, DFFF=descending flicker fusion frequency

Conclusion

Combined effects of piracetam and ginkgo biloba produced more significant effects than either *ginkgo biloba* or piracetam alone on cognitive function and working memory with regarding to the psychomotor performances in healthy young subjects.

Gingko Biloba in Tinnitus and sensorineural hearing loss[37]

Several uncontrolled or controlled but non-randomized clinical trials suggest that the regular medication with ginkgo biloba is effective in the treatment of tinnitus. Key data from these studies are summarized in Table 6.

Table 6: Efficacy studies of Gingko Biloba in Tinnitus and hearing loss

Author	Study details	Outcome
Meyer (1986)	• Multicentre RCT, double-blind, two parallel Groups • 103 patients with clinical tinnitus • 2×2 ml gingko biloba extract daily or Placebo • Primary end point: Severity score (0-3)	Significantly more patients in GBE group with marked improvement and faster reduction in symptoms
Meyer (1986)	• Multicenter RCT, three armed • 259 patients with tinnitus for 1 year or more • 3×3 ml gingko biloba extract daily or nicergoline or almitrine-raubasine for at least 1 month • Specialists evaluation	Significantly more patients in GBE group with marked improvement than in other two groups
Juretzek (1998)	• A (n=80): Open study without controls. B (n=20): RCT double-blind, two parallel Groups • 60 Patients with chronic tinnitus • 200 mg GBE by injection for 10 days followed by 2×80 mg daily oral GBE or placebo for 3 months • Primary endpoint: Loudness of Tinnitus	Significant improvement in GBE group compared with placebo, also for secondary endpoints like tinnitus frequency

Overall, the results of these trials are favorable to gingko biloba as a treatment for tinnitus

Effect of treatment with Ginkgo biloba extract EGb 761 (oral) on unilateral idiopathic sudden hearing loss in a prospective randomized double-blind study of 106 outpatients[38]

Burschka et al aimed to determine test of dose–response relationship for Ginkgo biloba extract EGb 761 (oral) in outpatients with acute idiopathic sudden sensorineural hearing loss (ISSHL) of at least 15 dB at one frequency within the speech range occurring less than 10 days before study inclusion.

Methods

- The study was a multicentre, randomized, double-blind phase III study comparing dosages of 120 mg twice daily and 12 mg twice daily over 8 weeks.
- Main endpoint: Recovery (in dB) of the auditory threshold from the initial measurement to the value on the last day of treatment, averaged over those frequencies from 0.25, 0.5, 1, 2, and 3 kHz for which the initial hearing loss amounted to 15 dB or more compared to the level on the opposite side.
- Patients: 106 patients with an average age of 44 ± 16 years and with hearing loss at affected frequencies 26 dB ± 9 dB included between December 1995 and July 1997.

Results

- Large majorities of both treatment groups recovered completely.
- In exploratory analyses of the 96 patients included according to the protocol, patients given the higher dose had less risk of not recovering well (≤10 dB residual hearing loss) (one-sided Fisher test: P = 0.0061), especially if they had no tinnitus (n = 44, P = 0.00702).

Conclusion

A higher dosage of EGb 761 (oral) appears to speed up and secure the recovery of ISSHL patients, with a good chance that they will recover completely, even with little treatment. This was already observed after one week of treatment. From the results of the study, it seems justified to treat patients who have unilateral ISSHL of less than 75 dB with 120 mg oral EGb 761 twice daily.

Oral extract of Gingko biloba appears to speed up and secure the recovery of idiopathic sudden sensorineural hearing loss patients, with a good chance that they will recover completely

Summary of studies on Gingko biloba for the treatment of cognitive impairment, vertigo, tinnitus and sensorineural hearing loss

Table 7 summarizes the efficacy studies on Gingko biloba for the treatment of cognitive impairment, vertigo, tinnitus and sensorineural hearing loss

Table 7: Summary of studies on Gingko Biloba in cognitive impairment and vertigo

Author	Outcome
Tan et al	EGb761 at 240 mg/day can stabilize or slow decline in cognition, function, behavior, and global change at 22–26 weeks in cognitive impairment and dementia, especially for patients with neuropsychiatric symptoms
Yang et al	Ginkgo biloba is potentially effective in improving cognitive function, activities of daily living, and global clinical assessment for patients with mild cognitive impairment or Alzheimer's disease.
Mix et al	There is complementary evidence of the potential efficacy of Ginkgo biloba EGb 7611 in enhancing certain neuropsychological/memory processes of cognitively intact older adults, 60 years of age and over.
Sokolova et al	There is evidence that the effect of Ginkgo biloba extract EGb761 is slightly more pronounced than the world's most frequently prescribed antivertiginous agent, betahistine, in the treatment of unspecified vertiginous syndromes
Alkuraishy et al	Combined effects of piracetam and ginkgo biloba produced more significant effects than either ginkgo biloba or piracetam alone on cognitive function and working memory with regarding to the psychomotor performances in healthy young subjects.
Meyer (1986)	Significantly more patients in GBE group with marked improvement and faster reduction in symptoms
Meyer (1986)	Significantly more patients in GBE group with marked improvement than in other two groups
Juretzek (1998)	Significant improvement in GBE group compared with placebo, also for secondary endpoints like tinnitus frequency
Burschka et al	Oral extract of Gingko biloba appears to speed up and secure the recovery of idiopathic sudden sensorineural hearing loss patients, with a good chance that they will recover completely

Vinpocetin

Vinpocetine is a synthetic ethyl ester of apovincamine, a vinca alkaloid obtained from the leaves of the Lesser Periwinkle (Vinca minor) and discovered in the late 1960s. Although used in human treatment for over twenty years, it has not been approved by any regulatory body for the treatment of cognitive impairment. Basic sciences studies have been used to claim a variety of potentially important effects in the brain. However, despite these many

proposed mechanisms and targets, the relevance of this basic science to clinical studies is unclear.[39] The clinical efficacy studies of vinpocetine in neurological disorders are summarized below.

Efficacy of vinpocetine in the management of cognitive impairment and memory loss[40]

Wollschlaeger et al aimed to determine the effect of Vinpocetine on objective measures of cognitive function and memory based on a critical review of the current literature.

Methods

The researchers attempted to identify all English and non-English-language articles in which Vinpocetine was used for the treatment of dementia, memory deficits, or cognitive impairment. The methodological quality of clinical trials utilizing Vinpocetine for cognition and memory enhancement was assessed. Trial outcomes were interpreted in relation to their quality and predefined criteria of good study methodology was used.

Results

- Of 39 articles reviewed only three met all inclusion criteria. In total 327 patients in the Vinpocetine or placebo group participated in the selected clinical trials.
- Overall there was a statistically significant improvement in the Clinical Global Impression (CGI) scale, Sandoz Clinical Assessment Geriatric (SCAG) scale, and Mini Mental Status Questionnaire (MMSQ) in the Vinpocetine treatment arm.
- No adverse events were reported, and side effects were mostly related to gastrointestinal discomfort.

Conclusion

Based on the selected clinical trials there is a significant effect of Vinpocetine in the management of cognitive impairment and memory loss in patients with early dementia or other related symptoms of cerebrovascular diseases.

Effect of Vinpocetine (Cognitol™) on Cognitive Performances[41]

Vinpocetine enhances cerebral utilization of oxygen and glucose and consequently improves cerebral functions including memory.

Ogunrin et al assessed the efficacy of vinpocetine (Cognitol™) in improving memory and concentration in cognitively impaired patients.

Methods

The study protocol is described in Figure 19

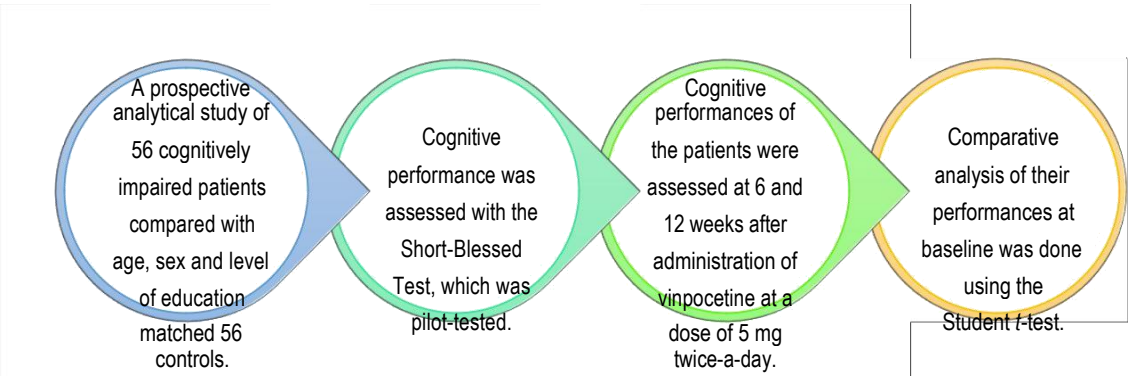

Figure 19: The study protocol

Results

- The mean (standard deviation) [SD] ages of the cognitively impaired patients (56/112) and controls (56/112) were 49.5 (18.9) and 53.8 (15.8) years respectively ($P = 0.19$; 95% confidence interval [CI]: 2.2-10.8) (Figures 20 and 21).
- The pilot study yielded an optimal cut-off error score of 6 with a sensitivity of 71.4%, specificity of 96.4% and accuracy of 83.9%.
- Patients performed significantly worse than the controls ($P < 0.001$; 95% CI 6.7-11.4).
- There were significant improvements in memory and concentration with vinpocetine therapy ($P< 0.05$).
- The clinical variables of the patients had no effect on the trend of cognitive performances.

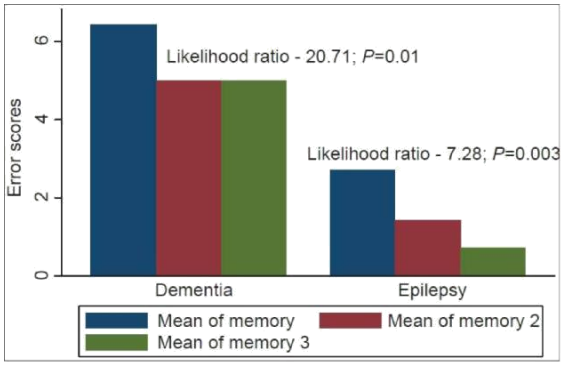

Figure 20: Bar chart showing memory error scores for patients with epilepsy and dementia. Mean of memory 1: Mean error scores at baseline; mean of memory 2: Mean error scores at 6 weeks; mean of memory 3: Mean error scores at 12 weeks

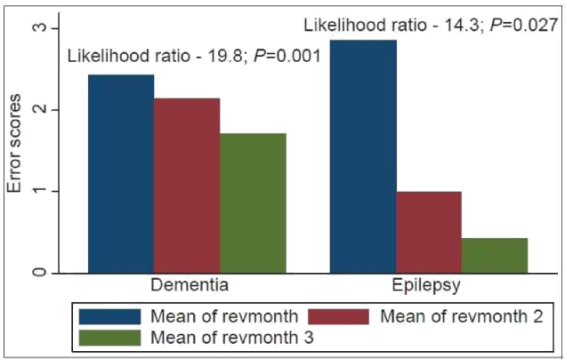

Figure 21: Bar chart showing concentration error scores for patients with epilepsy and dementia. Mean of revmonth 1: Mean error scores at baseline; mean of revmonth 2: Mean error scores at 6 weeks; mean of revmonth 3: Mean error scores at 12 weeks

Conclusion

Vinpocetine was effective in improving memory and concentration of patients with epilepsy and dementia

Vinpocetin in neurological diseases[42]

Vinpocetin appears to have several different mechanisms of action that allow for its antiinflammatory, antioxidant, vasodilating, antiepileptic and neuroprotective activities in experimental conditions. Conversely, several meta-analyses of the existing studies in acute stroke examining short and long-term fatality rates with vinpocetin was unable to assess efficacy.

Szapáry et al aimed to review the experimental and clinical articles focusing on the role of vinpocetin in different neurological conditions.

Results

In chronic cerebrovascular patients, vinpocetin improved impaired hemorheologic variables, showed significant vasodilating properties, improved endothelial dysfunction, neuroimaging studies showed selective increase in cerebral blood flow and cerebral metabolic rate, all of which are potentially beneficial in cerebrovascular disease and may improve cognitive functions.

Conclusion

Based on the above mentioned results, vinpocetin plays an important role both in basic research and in clinical management of different neurological diseases

Clinical study of vinpocetine in the treatment of vertigo[43]

Taiji and Kanzaki aimed to evaluate the therapeutic effects of vinpocetine after the administration of drug for 4 weeks or more to 44 patients with vertigo (aged 18-76).

Results

- As to the subjective symptoms, 'vertigo' was improved in 100% of patients, 'dizziness' in 71%, and equilibrium disturbance' in 52%, 'nausea and/or vomiting' were reduced in 90% of patients, 'stiff shoulder' in 62%, and 'heavy head and/or headache' in 67%.
- As to the objective symptoms, the improvement was obtained in 100% for the spontaneous nystagmus test, in 80% for the positional nystagmus test, and in 54% for the stepping test.
- The percentage of patients with satisfactory overall improvement was 77% (marked 23%, moderate 54%).

Conclusion

These results suggest that vinpocetine is effective for the treatment of vertigo with less side effect.

Efficacy studies on Vinpocetin for the treatment of cognitive impairment, vertigo and neurological disorders

Table 8 summarizes the efficacy studies on vinpocetine for the treatment of cognitive impairment, vertigo and neurological disorders.

Table 8: Summary of studies on Vinpocetin in cognitive impairment and vertigo

Author	Outcome
Wollschlaeger et al	Vinpocetin had a significant effect in the management of cognitive impairment and memory loss in patients with early dementia or other related symptoms of cerebrovascular diseases.
Ogunrin et al	Vinpocetine was effective in improving memory and concentration of patients with epilepsy and dementia
Szapáry et al	Vinpocetin plays an important role both in basic research and in clinical management of different neurological diseases.

Taiji and Kanzaki	Vinpocetine was found to be effective for the treatment of vertigo with less side effect.

Thus, based on the outcomes of clinical trials on piracetam, gingko biloba and vinpocetine, it can be concluded that there is promising evidence of improvement in cognition and other neurological functions associated with piracetam, gingko biloba and vinpocetine. Also, these entities appeared to be safe and well-tolerated in most of the studies. Thus, a combination of these entities may be an effective option in mild cognitive impairment and other neurological conditions.

A combination of piracetam, gingko biloba and vinpocetine may be a safe and effective option in mild cognitive impairment and other neurological conditions.

Conclusion

- **The World Health Organization estimates that 35.6 million people live with dementia, a number that is anticipated to triple by 2050**
- **Cognitive impairment associated with cerebrovascular disease is an increasingly important and recognized area of the medicine of older people**
- **Vascular cognitive impairment can present with mild deficits affecting one cognitive domain or advanced cognitive impairment**
- **Blood pressure lowering may have some beneficial effects on cognitive decline, but it is not yet clear whether it prevents cognitive decline through other mechanisms**
- **Statin therapy in secondary stroke prevention has shown an effect on new vascular events but only marginally reduces the risk of stroke recurrence**
- **Exercise training is standard for cardiovascular disease management, and cardiac rehabilitation was shown to improve cognitive performance in several studies**
- **Piracetam is a drug that may enhance memory and other intellectual functions through mechanisms which are ill-understood and still debated**
- **Beneficial effects of piracetam on learning and memory have been demonstrated in several animal studies including some on older animals**
- **Ginkgo biloba is recommended for age-related cognitive decline and for slowing the progress of neurodegenerative disorders such as Alzheimer's disease and for other forms of dementia**
- **Vinpocetine, chemically known as ethyl apovincaminate, is a vinca alkaloid that exhibits cerebral blood-flow enhancing and neuroprotective effects**
- **To date, there is no effective modifying therapy for the treatment of dementia. Nonetheless, combination therapy holds promise, and nutraceuticals and their synthetic derivatives are well-tolerated candidates**

- **Menière's syndrome is a chronic inner-ear disorder characterized by recurrent episodes of spontaneous vertigo and fluctuating unilateral sensorineural hearing loss (SNHL), tinnitus, and aural fullness.**
- **There is compelling evidence for the global clinical efficacy of piracetam in a diverse group of older subjects with cognitive impairment**
- **Piracetam benefits written language ability at the end of trials, which could be a potential target for further research**
- **Piracetam caused significant improvement in vertigo and spontaneous and positional nystagmus in patients with post-concussional vertigo and headache**
- **As compared to placebo, piracetam caused a significant improvement in the frequency and severity of episodes of vertigo, in tinnitus and in social and professional functioning**
- **There was significant improvement after piracetam: episodes of vertigo were significantly less frequent, and the duration of incapacity was less**
- **Piracetam, which improves rheology and has a positive effect on metabolism, would appear of interest for the treatment of acute tinnitus.**
- **Piracetam seemed to be effective in this sensorineural deafness, probably because of its effect on the viscoelastic properties of blood.**
- **Piracetam caused a rapid recovery of hearing loss and did not cause any side effects.**
- **Piracetam helps in reducing tinnitus and improve sensorineural hearing loss in patients with tinnitus and the treatment should continue as long as tinnitus persists**
- **Extract of Gingko biloba at 240 mg/day can stabilize or slow decline in cognition, function, behavior, and global change at 22–26 weeks in cognitive impairment and dementia, especially for patients with neuropsychiatric symptoms**
- **Ginkgo biloba is potentially effective in improving cognitive function, activities of daily living, and global clinical assessment for patients with mild cognitive impairment or Alzheimer's disease.**
- **There is complementary evidence of the potential efficacy of Ginkgo biloba in enhancing certain neuropsychological/memory processes of cognitively intact older adults, 60 years of age and over.**
- **There is evidence that the effect of Ginkgo biloba extract is slightly more pronounced than the world's most frequently prescribed antivertiginous agent, betahistine, in the treatment of unspecified vertiginous syndromes**
- **Combined effects of piracetam and ginkgo biloba produced more significant effects than either ginkgo biloba or piracetam alone on cognitive function and working memory with regarding to the psychomotor performances in healthy young subjects.**
- **Significantly more patients in GBE group with marked improvement and faster reduction in symptoms**
- **Significantly more patients in GBE group with marked improvement than in other two groups**
- **Significant improvement in GBE group compared with placebo, also for secondary endpoints like tinnitus frequency**

- **Oral extract of Gingko biloba appears to speed up and secure the recovery of idiopathic sudden sensorineural hearing loss patients, with a good chance that they will recover completely**
- **Vinpocetin had a significant effect in the management of cognitive impairment and memory loss in patients with early dementia or other related symptoms of cerebrovascular diseases.**
- **Vinpocetine was effective in improving memory and concentration of patients with epilepsy and dementia**
- **Vinpocetin plays an important role both in basic research and in clinical management of different neurological diseases.**
- **Vinpocetine was found to be effective for the treatment of vertigo with less side effect.**

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