

Complementary Medicines in Dementia / Alzheimer's Disease

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Overview

- This presentation will explore some of the complementary medicines and complementary therapies used in the prevention and management of patients with dementia and Alzheimer's disease
- It will also investigate the evidence to support use of selected CMs for this indication, as well as appropriate place in therapy



CAM in Dementia /Alzheimer' Disease

- Frequently used, often with unrealistic expectations
- Confusion: What works, what doesn't, when to use what?
- Current rate of CAM use is greater than rate of research and knowledge in dementia/Alzheimer's disease
- Evidence-based data useful – but not everything
- Also consider the limitations with currently available drug therapies
- Never underestimate the difference a small change can make for an individual or their family

Treatment



Complementary Medicines in Treatment of Dementia / AD

Therapy	Specific therapeutic use	Quality of evidence
Ginkgo	Dementia / Alzheimer's disease treatment	Good positive scientific evidence
Korean ginseng	Alzheimer's disease – cognitive function and psychomotor performance	Good positive scientific evidence
Chocolate	Improved cognitive performance	Scientific evidence, but studies limited
Caffeine	Cognitive performance	Scientific evidence, but data in humans limited
Melatonin	Improves circadian rhythm disturbances	Scientific evidence, but unclear/conflicting
Sage	Cognition; may reduce agitation	Scientific evidence, but studies limited
Lecithin	Cognition	Scientific evidence, but studies limited and conflicting
Bacopa	Cognition	Evidence lacking in dementia/AD based on limited study



Ginkgo

- One of the world's oldest living tree species
 - Can be traced back >200 million years before the Ice Age.
- Used medicinally for thousands of years
- One of most highly prescribed herbal therapies in Europe.
- Been reported as **top selling herbal medicine in USA** , with sales of **US\$ 148 million** (1999)



Ginkgo

Evidence conflicting and inconsistent, however, based on current data is suitable as:

- **Treatment** of mild-mod Alzheimer's disease (AD) / dementia (adjunctive therapy)
- **No evidence that prevents AD/dementia**

- Ginkgo shown to **improve daily living activities and cognitive function** in people with **mild-moderate cognitive impairment / Alzheimer's Disease** *(Janssen et al 2010)*



Ginkgo



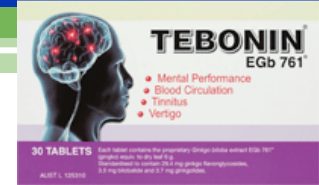
- Ginkgo (EGb761) slows decline in cognition, function, behaviour and global change at 22-26 weeks in cognitive impairment & dementia, especially in patients with neuropsychiatric symptoms

(Tan et al 2014)

- Review of 9 RCT (n=2 561) trial duration 22-26 weeks
- Safety data revealed no important safety concerns



Ginkgo



- Ginkgo (EGb761) shown to be significantly **superior to placebo** in Tx of patients with mild to moderate dementia **with neuropsychiatric symptoms** (Ihl 2011)

- Clinically significant improvements in all neuropsychiatric scores with EGb761 compared to placebo
- (n=410; 24 weeks study, 240mg/day EGB761)
- Adverse effects similar to placebo

- Clinical efficacy for ginkgo EGb761 (160mg /day) was found to be **comparable to donepezil** (50mg/day) in dementia of Alzheimer's type in RCT (Mazza et al 2006)



Ginkgo - Safety concerns

- **Adverse effects:**
 - Headache, nausea, GI complaints (low incidence, comparable to placebo)
 - Case reports of unexplained bleeding
 - However, no clinically significant effects on bleeding or changes to platelet function or blood coagulation factors reported in a review of 8 clinical studies (Savovic et al 2005)
- **Contraindications, warnings & precautions**
 - Patient should stop Tx and report if any unusual bruising or bleeding



Ginkgo - Key drug-herb Interactions

Alzheimer's drugs	Additive effects possible	Potentially beneficial
Antipsychotic drugs	Additive effects possible	Potentially beneficial, needs medical supervision
Hypoglycaemic drugs	May affect blood glucose levels, but data limited	Caution – possible risk
Warfarin, aspirin, antiplatelet drugs	May theoretically increase risk of bleeding , but data conflicting. No clinically significant interaction according to systematic review (<i>Bone 2008</i>)	Caution – moderate risk, medical supervision and monitoring required if use
Anticonvulsants	Case reports of reduced drug effect – increased risk seizures	Concurrent use not advised



Korean Ginseng (Panax)



- **Improve cognition when used as adjunct therapy to conventional drug therapy in AD**
- **Significant cognitive improvement** in patients with Alzheimer's disease as adjunct therapy
 - Against ADAS-cog and Clinical Dementia rating (CDR) scales.
 - Max benefits seen **after 24 weeks of therapy**.
 - **Effects sustained** with ongoing treatment for a **two year** follow-up period
(Heo et al 2011)
- **Clinically significant improvements in cognitive performance in AD patients** (compared to placebo) against:
 - Mini-Mental Status Examination (**MMSE**) and Alzheimer's Disease Assessment Scale (**ADAS**)-cognition.
 - **Improvements seen after 12 weeks**, but scores **returned to baseline after discontinuation** of ginseng therapy *(Lee et al 2008)*



Panax Ginseng - Safety concerns

Low incidence of reported adverse effects

- **GI effects** – Nausea (best to take after food), GI discomfort, diarrhoea
- **Overstimulation** in excess dosage (best to avoid taking late afternoon / evening)

Precautions

- **Caution** in patients with **diabetes**
 - *(dose adjustments may be needed)*
- **Caution** in patients with **CV disorders**
 - *(dose adjustments may be needed)*
- **Caution** with **hormone-related cancers**
 - *(oestrogenic effect observed)*
- **Long term use not generally recommended**
 - *supervision needed if using longer term in AD patients*
- May **interact with stimulants** including **caffeine**



Not specifically in
AD/Dementia patients



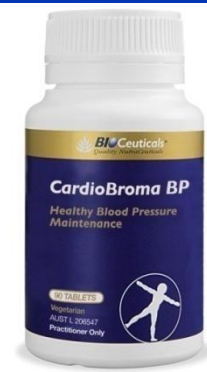
Chocolate / Cocoa

- Improved cerebral blood flow and cognitive performance (attention & memory) seen with Chocolate (as 2 cups cocoa/day for 2 weeks)
 - (n=34 elderly volunteers) (*Sorond et al 2008*)
- Regular consumption of dietary cocoa led to an improvement in cognitive function (MMSE test A and B) and verbal fluency test scores
 - Study of 90 elderly patients with mild cognitive impairment;
 - Improved insulin resistance, BP and lipid peroxidation also reported
 - Best response in those with highest intake of cocoa flavanols/day compared to placebo (*Desideri et al 2012*)

Of interest – cocoa was shown to have neuro-protective effects in a study in children (*Calderon-Gardiduenas et al 2013*)



Contains
*Theobroma
cacao*



Chocolate / Cocoa

- Chocolate also shown to have CV benefits (lowers BP, lowers risk of stroke and may have a positive effect on insulin resistance

(Hooper et al 2012, Larsson et al 2012)

- Moderate chocolate consumption may lower risk of stroke according to a prospective study of >37 000 men over 10 years

(Larsson et al 2012)

- One study showed chocolate associated with a substantial reduction in cardiometabolic disorders including 37% reduction in CVD and 29% reduction in stroke in those with highest chocolate consumption

(meta-analysis involving >114 000 participants; Buitrago-Lopez et al 2011)



Chocolate - How does it work?

- Contains flavonoids with potent **antioxidant and anti-inflammatory** activity
- **Neuroprotective and neuromodulatory mechanisms**
 - Interacts with cellular cascades to support expression of proteins that promote the synthesis of neurons, neuronal function and brain connectivity
 - Improved cerebral blood flow and development of new blood vessels in brain and sensory systems
 - Inhibition of neuronal death due to neurotoxins such as oxygen radicals
 - Promotes neuronal survival
 - Flavonoids in cocoa shown to **preserve cognitive abilities** in animal studies

(Sokolov et al 2013; Nehlig 2013)



Caffeine

- Long history as cognition enhancer
 - Beneficial effects shown on psychomotor activity in patients with hypoactive delirium and cognitive disorders (Mercadante et al 2010)
 - Epidemiologic studies have also suggested caffeine / coffee may reduce Alzheimer's disease risk (Dostal et al 2010)
- Protective effects against memory impairment reported in animal study.
 - Aged cognitively impaired mice also exhibited memory restoration and lower brain amyloid-beta levels after 1-2 months caffeine Tx
 - Doses used were equivalent to **500mg caffeine/day in adults = 5 cups coffee/day.** (Arendash et al 2010)



Caffeine - How does it work?

- Protective effects of caffeine against Alzheimer's disease seems due to
 - Antagonism of adenosine receptors
 - Actions on dopamine and other neurotransmitters
 - Reduced production of amyloid-beta

- More human studies needed to determine place in therapy
- However current research positive
- Caffeine (as coffee) may potentially have a benefit in both treatment and prevention



Melatonin

- Available in Australia on prescription – Circadin® 2mg
- Note registered only for short term insomnia in elderly in Australia
- Homeopathic melatonin (in pharmacy OTC and health food shops) highly unlikely to be of benefit!!
- May be useful for disturbances in circadian rhythm in dementia
- Some, but not all studies have found benefit in **improving sundowning, sleep / night cycle and agitated behaviour**
(de Jonghe 2010)

Dose will be 'X'
or 'C' not mg/g



Sage

Sage also used as aromatherapy oil

- Use of Sage herbal medicine in patients with mild-mod AD for 4 months prevented deterioration of cognition and reduced agitation (*Akhondzadeh et al 2003*)
- Sage appears to have anticholinergic activity
- Also shown to improve mood and cognition in healthy individuals
- Insufficient evidence to support wide-spread use
- Might be a useful choice if having aromatherapy (massage, bath, candle / oil burner etc)



Lecithin - Dietary source of choline

- People with AD may lack enzyme responsible for converting choline to acetylcholine in brain
- Thought that consumption of lecithin may potentially reduce progression of dementia
- Been an area of interest since 1970's
- But lack of quality data to confirm or refute effects
- Review of 12 RCT showed that there is no enough evidence to support use of lecithin in the treatment of patients with dementia/ AD

(Higgins and Flicker 2003).

- Some studies have shown substantial improvement of memory and behavioural measures – other studies shown no benefit
- Possible that an individual may have benefit – as adjunct therapy
- Most studies been in combo with tacrine



Bacopa

- Traditionally used to enhance cognition and memory
- **Lack of evidence in dementia or AD**
- Limited evidence suggests possible cognitive benefit in healthy individuals.
- Will not prevent cognitive decline



Complementary and Alternative Therapies in Dementia / AD

Therapy	Specific therapeutic use	Quality of evidence
Aromatherapy e.g. Lemon balm, lavender	May reduce agitation in dementia; excessive motor behaviours; better as massage than only as scent	Good evidence seen in the few studies conducted
Light therapy	May improve insomnia, behavioural and psychiatric disturbances Calming effect seen on agitated patients	Good preliminary scientific evidence, but only limited studies conducted
Music therapy	Improved communication skills; Improved MMSE scores after music; Improved positive engagement; Decreased agitation and aggression	Good scientific evidence, although benefits do not seem long lasting



Complementary and Alternative Therapies in Dementia / AD

Therapy	Specific therapeutic use	Quality of evidence
Acupuncture (mainly for vascular dementia)	Dementia, memory loss, disorientation, cognitive disorders	Some positive evidence, but results not clear
Massage / therapeutic touch	May reduce agitation; May encourage eating (when combined with verbal encouragement)	Benefits possible, but very limited research has been conducted
Pet therapy	Alzheimer's dementia – shown to improve social behaviours; reduces agitation	Benefits possible – more study needed

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Prevention



Complementary Medicines in Prevention of Dementia / AD

Therapy	Specific therapeutic use
Omega-3 fatty acids/ fish oils	DHA deficiency linked to increased risk of dementia / AD. Supplements may reduce incidence of Alzheimer's disease and cognitive impairment
Vitamin D	Deficiency increases risk of dementia Alzheimer's disease
Chromium (nutrient needed for blood sugar regulation)	Impaired glucose metabolism and insulin resistance may be linked to cognitive decline, dementia, Alzheimer's disease (more data needed to confirm specific role)
Caffeine	May reduce risk based on recent evidence

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Complementary Medicines in Prevention of Dementia / AD

Therapy	Specific therapeutic use
Folate	Low blood folate levels associated with increased prevalence of AD; Higher dietary intake / higher serum levels of folate associated with reduced risk of AD and dementia in some studies
Vitamin B3 (niacin)	Higher dietary intake seems to have a neuroprotective effect in AD development and cognitive decline
Vitamin B12	Lower levels seen in patients with AD. Effects of B12 supplementation on prevention or progression of AD unclear
Beta-carotene	Inconsistent relationship between low dietary intake and AD risk
Vitamin C	Limited study – but may have protective effect against AD
Vitamin B6	Association NOT seen between low B6 and AD; may affect cognition in healthy individuals

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Omega-3 Fish oils and Alzheimer's dementia



- Regular fish oil consumption may decrease risk of dementia according to epidemiological data *(Nat Std 2014)*
- Low DHA (omega-3 fatty acid) levels linked to development of Alzheimer's disease
- Research also suggests risk factors for Alzheimer's disease similar in many respects to risk factors for CVD
 - This includes diet with imbalance between ratio of omega-6 fatty acids: Omega-3 fatty acids
 - Should be ratio of 4:1; but modern diet gives us ratio of 20:1



Omega-3 Fish oils and Alzheimer's dementia



- This relative deficiency in omega-3's has been associated with multiple potential health consequences
 - Cardiovascular disease
 - Alzheimer's disease / senile dementia
 - Rheumatoid arthritis
 - Depression
 - Some cancers
 - Other inflammatory disorders
 -others
- **Omega-3 fatty acids** found oily fish such as salmon, mackerel, herring and sardines
 - **Omega-6 fatty acids** found in vegetable oils e.g. Sunflower, safflower, grapeseed, cooking oil blends, soyabean, mayonnaise, salad dressing, margarine, nuts, seeds etc



Omega-3 Fish oils and Alzheimer's dementia

- Supplemental Omega-3 fish oils may **reduce incidence of Alzheimer's disease and cognitive impairment**, although trial results conflicting
- More study needed *(Sydenham et al 2012; Freund-Levi et al 2006)*

- Place in therapy would be for **prevention, not treatment**
- Most benefits appear to be due to **DHA**
- A DHA-enriched omega-3 supplement may positively affect weight and appetite in patients with mild to moderate AD *(Irving et al 2009)*

Omega-3 Fish oils and Alzheimer's dementia



Bottom line? To take or not for AD prevention?

- No clear answer based on evidence alone.....
- However... Since Omega-3's have also shown to have clinically significant benefits in other diseases associated with aging e.g.
 - Hypertension
 - Hyperlipidaemia
 - Reduction in CVD risk
 - Rheumatoid arthritis

Dose should be based on EPA/DHA content, potency varies with different brands

The overall benefits seem to outweigh the risks



Vitamin D

- Vitamin D deficiency associated with substantially increased risk of all-cause dementia and Alzheimer's disease
 - Findings of a recent 5 year study (1658 elderly patients)

(Littlejohn et al 2014)

- Adequate Vitamin D can be obtained via sun exposure
- However, supplemental Vitamin D may be required in some patients
- Given as Vitamin D3 (cholecalciferol) (e.g. Ostelin®)
- Vitamin D supplements are well tolerated



Vitamin D Deficiency

- Estimated that 1 billion people world wide have a vitamin D deficiency
- Studies show that >30% of adult Australians are Vitamin D deficient
 - Attributed mainly to less sun exposure due to climate, lifestyle, concerns about skin cancer

Success of the Slip, Slop, Slap campaign

- Can assess Vitamin D status with blood test



Vitamin D

How much sun do you need?

- Adequate Vitamin D levels achieved with sun exposure to bare skin, such as arms and legs:
 - Summer - about 6-8 minutes exposure - most days of the week
 - Winter – 7-40 minutes exposure - most days of week (depends on factors such as latitude)
 - Best mid -morning or mid-afternoon.



Vitamin D - Risk Groups

Main risk groups for Vitamin D deficiency

- Older or disabled people, hospitalised or housebound
- People with naturally dark skin
- Women who cover most of their body for religious or cultural reasons
- People that work in enclosed environments e.g. offices, factories, warehouses or night shift workers
- Fair skinned people who deliberately avoid sun exposure, e.g. due to risk of skin cancer
- People who are obese, or have chronic disease states such as multiple sclerosis, or have malabsorption syndromes

Diet - General guidelines for prevention of AD/dementia



High in saturated fats	Increased risk age-related cognitive decline & mild cognitive impairment
Low consumption milk and dairy	Increased risk vascular dementia
High consumption whole-fat dairy	Possible increase in cognitive decline in elderly
High in fish, omega-3 fatty acids	Decreased risk cognitive decline, dementia
Light-to-mod intake of alcohol (wine)	Decreased risk incident dementia and AD
High fruit and vegetables	Protective role against cognitive decline, dementia, AD; antioxidant intake
High antioxidant diet	Protective effect, especially foods with high anthocyanidin content to maintain brain function (e.g. berries, cherries, red grapes, acai berry, pomegranate)
Mediterranean diet	Protective effect against dementia & pre-dementia; slower cognitive decline; reduced risk of progression from MCI to AD, reduced risk AS and all-cause mortality in AD



Antioxidants

Antioxidants prevent damage that occurs in cells and body tissues due to both normal bodily processes and exposure to some chemicals and environmental factors.

Why do we need antioxidants?

- Normal oxidation reactions in body, as well as chemicals and environmental factors produces what are known as "free radicals."
- These reactions are critical for the body to function.
- However, the cumulative effect of too many oxidation reactions may irreversibly damage the body.
- Humans therefore need a variety of **ANTI-OXIDANTS** to **reduce the impact of the free radicals created by these oxidation reactions.**
- If the body has **too few antioxidants**, then the stress of many oxidation reactions may **damage or kill body cells.**
- If enough cells are killed or damaged....**results in illness or disease**
- Antioxidants work **best in combination** (variety of antioxidant foods, and/ or in supplements with a combination of antioxidant nutrients)

Examples of Foods high in antioxidants

- Blueberries
- Cranberries
- Blackberries
- Raspberries
- Strawberries
- Cherries
- Red grapes
- Pomegranate
- Carrots
- Papaya
- Citrus fruits

High in
anthocyanidins
Neuroprotective

- Dark chocolate / cocoa
- Green tea
- Apples
- Plums
- Leafy greens
- Tomatoes
- Red kidney beans
- Black beans
- Artichokes
- Onions
- Broccoli
- Garlic

Flavanols

More Information?



Curtin Library - LibGuide on CAMs

- >> Go to Library Home page
- >> LibGuides (under Top Links (RHS))
- >> Health Science (from banner along top)
- >> Specialised Health LibGuides (at bottom page)
- >> Complementary and Integrative Medicine LibGuide
- >> has links to books, journals, databases, websites etc on CAMs



Natural Standard Databases

Excellent CAM resource if you have access to Curtin Library
Library >>Databases>> Natural Standard

- **Foods, Herbs & Supplements**
- Health and Wellness
- **Comparative Effectiveness**
- Brand Names
- Charts and Tables
- Medical Conditions
- Sports Medicine
- Genomics and Proteomics
- Environment and Global Health

Detailed monographs,
evidence charts,
evidence discussion
with hyperlinks to links
to references

Compares the
evidence of various
CM therapies for a
given condition.

Subscription database – so not able to access
unless able to login to Curtin Library



Key Databases

About Herbs

- Free App to download 'About Herbs'
- Useful tool for medical staff and carers who are looking for a reputable, reliable resource on CMs
- Not only on Herbs! Also has Nutritional and other CAM information
- Originally developed as a resource for CAMs in cancer by **Memorial Sloane Kettering Hospital**
- www.mskcc.org/mskcc
- No longer only cancer site now - also has other general evidence-based information on CAMs.





Key databases

Cochrane Library

- www.cochrane.library.com
- International network that provides evidence-based medicine reviews
 - Under "Browse by topic" on column left of screen, tab on 'Complementary And Alternative Medicine' to see reviews by disease state.

Cochrane Reviews

- www.cochrane.org/cochrane-reviews
 - Search for reviews on individual complementary or alternative medicines (e.g. Ginkgo)



Key Databases

The National Center for Complementary and Alternative Medicine (NCCAM) - USA

- www.nccam.nih.gov
- Leading USA agency for scientific research on the diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine.
- Provides comprehensive information for both consumer and health professional



Key databases

USA - National Institute of Health (NIH)

www.ods.od.nih.gov

- Homepage of the U.S. Office of Dietary Supplements. Comprehensive database with information of nutrition and nutritional supplements

www.nlm.nih.gov/medlineplus/druginformation

- Summaries of many herbal supplements collected by the U.S. National Library of Medicine and National Institute of Health.

Thank You