



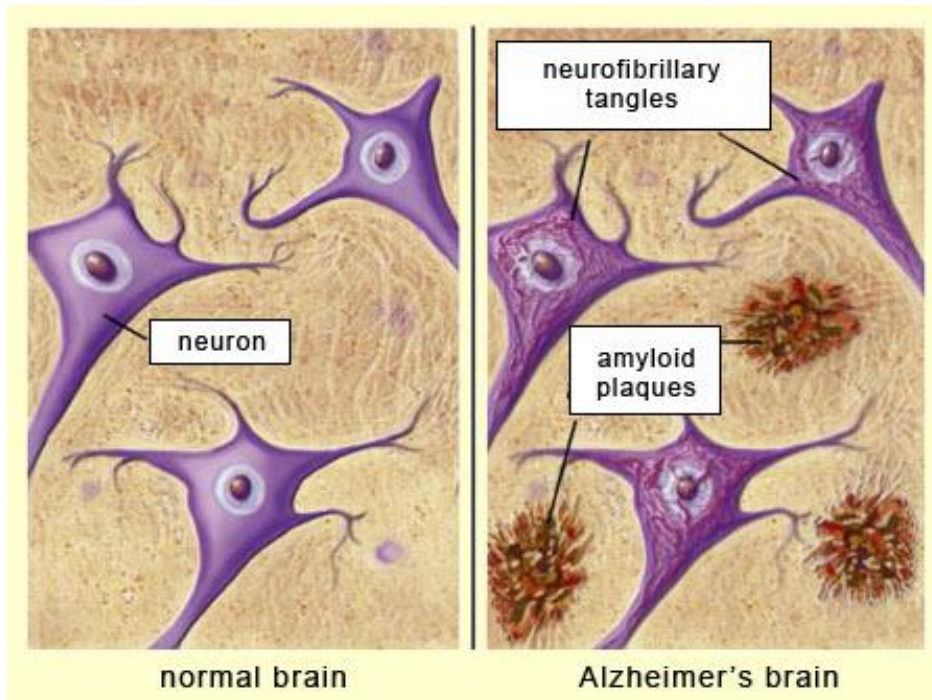
Nonpharmacological interventions in Alzheimer's disease. An Update

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○ No disclosures.

Alzheimer's Dementia



amyloid plaques and neurofibrillary tangles. neuronal connectivity is affected → progressively leading to neuronal death

- Progressive cognitive decline in addition to psychological disturbances, changes some behavioral patterns and impairments in performing daily function which affects > 5.4 million Americans.
- Impact QOL
- Major cause of institutionalization and mortality
- Risk factors : Obesity, diabetes, hypertension and inflammation (11-14)

Complications of Alzheimer's Dementia : **Agitation**

- Can lead to lost work and financial burdens with family members and caregivers.
- 1st & 2nd generation Antipsychotics have side effects: CV disease, stroke, falls, increased mortality

Howland RH. Risk and benefits of antipsychotic drugs in elderly patients with dementia. J Psychosoc Nurs Ment Health Serv. 2008; 46 : 19-23

Non pharmacological approaches

- Non invasive
- Fewer side effects
- Safer to use.

Adjuvant therapies

- It is important to note the presence of certain unsubstantiated claims regarding the use of certain alternative therapies that make both patients and caregivers wary about considering some approaches (44).



Lifestyle modification with physical activity: Cochrane Review February 2015

- 17 trials (search dates August 2012 and October 2013),
- 1,067 participants, that tested whether exercise improved

+ cognition (which includes such things as memory, reasoning ability and spatial awareness)

— **activities of daily living**

psychological symptoms (such as depression, agitation)

mortality

quality of life

caregivers' experience

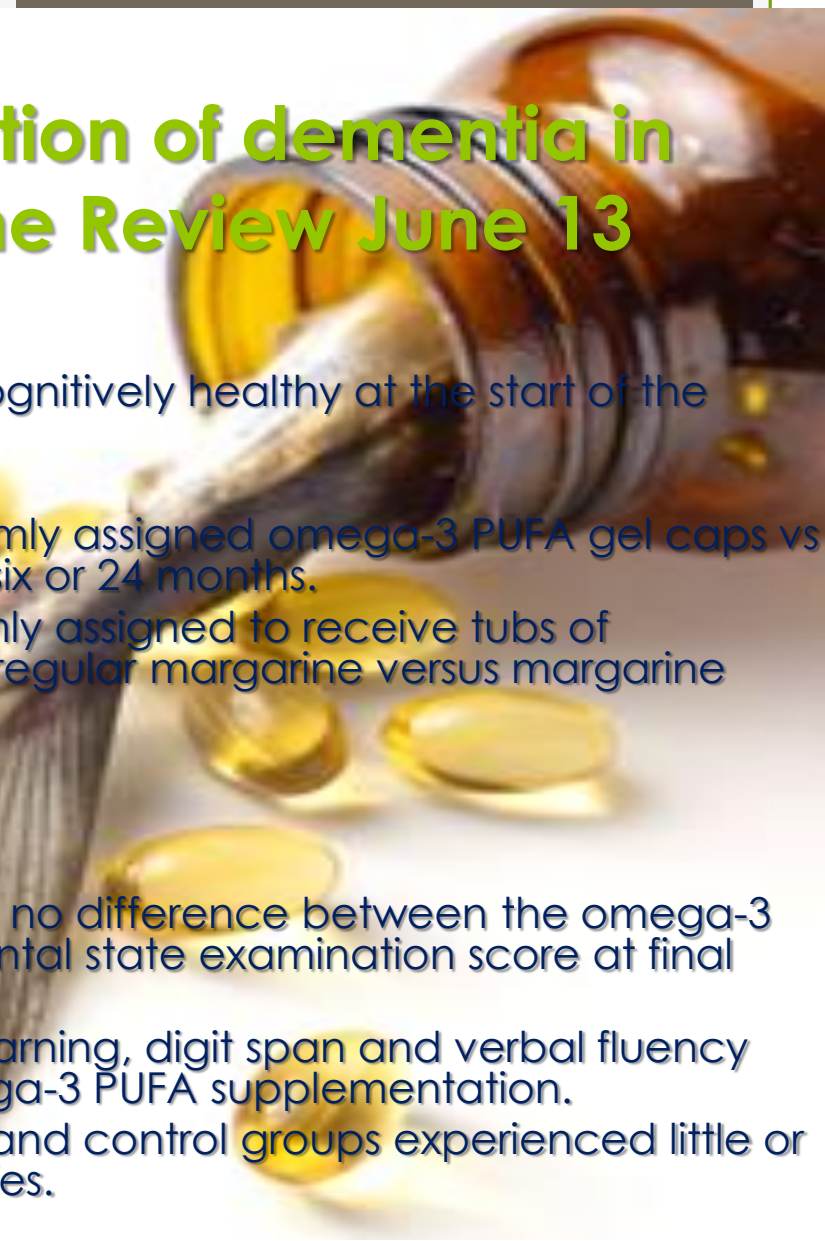
use of healthcare services

adverse effects of exercise.



Fish oils for the prevention of dementia in older people Cochrane Review June 13 2012

- Participants : healthy , > 60 years , cognitively healthy at the start of the study
- 3 RCT involving 3536 participants.
 - 2 studies participants were randomly assigned omega-3 PUFA gel caps vs olive or sunflower oil gel caps for six or 24 months.
 - 1 study, participants were randomly assigned to receive tubs of margarine spread for 40 months (regular margarine versus margarine fortified with omega-3 PUFA).
- outcomes of interest
 - new cases of dementia
 - cognitive decline
- 2 studies involving 3221 participants : no difference between the omega-3 PUFA and placebo group in mini-mental state examination score at final follow-up.
- 2 studies (1043 participants), word learning, digit span and verbal fluency showed no beneficial effect of omega-3 PUFA supplementation.
- Participants in both the intervention and control groups experienced little or no cognitive decline during the studies.



Reminiscence therapy for Dementia

Cochrane review April 20 2005

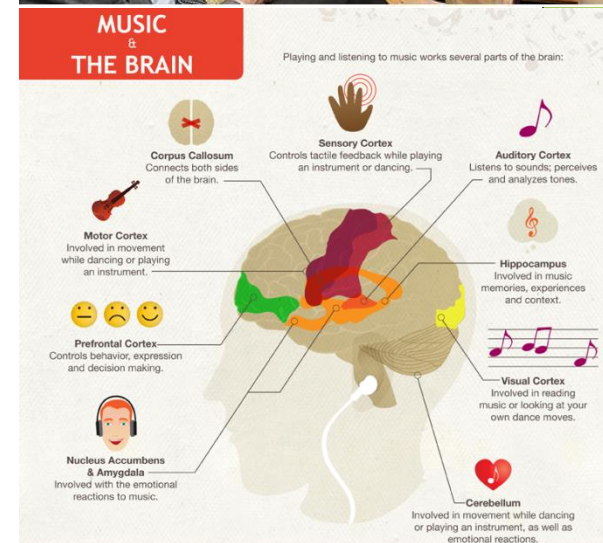
- Involves discussion of past activities, events and experiences, with another person or group of people.
 - Aids are used such as videos, pictures, archives and life story books.
- 4 RCTs
 - cognition and mood improved 4 to 6 weeks after the treatment,
 - care-givers participating with their relative with dementia in a reminiscence group reported lower strain,
 - people with dementia were reported to show some indications of improved functional ability.
 - No harmful effects
 - However, in view of the limitations (very small studies or were of relatively low quality) of the studies reviewed, there is an further need for more quality research in the field.



Music therapy: Cochrane Review:

Annemiek C Vink^{1,*}, Manon S Bruinsma², Rob JPM Scholten³ Editorial Group [Cochrane Dementia and Cognitive Improvement Group](#), Published Online: 20 OCT 2003/ Assessed as up-to-date: 12 APR 2010

- The specific focus was to assess whether music therapy can diminish behavioral and cognitive problems or improve social and emotional functioning.
- 10 studies
- The methodological quality and the reporting of the included studies were too poor to draw any useful conclusions.



SOURCES: lifehacker.com | cerebrocentris.org.br | wired.com | news-medical.net | en.wikipedia.org | quantumjumping.com | psychologytoday.com/blog/memory-medic/ | slgate.com | theglobeandmail.com



Aromatherapy

Yield relaxation and decreased agitation



- Lavender & Lemon balms are commonly used.
- Absorption of essential oil via
 - Trans-dermally vs Inhalation
- Activates autonomic nervous system : Induce reaction in the limbic system and hypothalamus. Mechanism of action is still not fully understood.
 - promote sleep and ameliorate agitation, and improve QOL in dementia.
 - Anxiolytic effects of aromatic oils suppress dopamine via enhancing serotonergic neuronal activity
- Lavender oil : improves poor sleep patterns and increases sleep , reduces excessive motor activity and agitation.
- Multiple exposures of lavender oil reversed spatial memory deficits , positive effects on memory formation
- Lemon, rosemary and peppermint aromatherapy may produce similar effects as well.
- Jimbo, et al (90) identified that effects of a cocktail of essential oils stimulates bot the sympathetic and parasympathetic nervous system of AD and improves the ability to form abstract ideas, conceptual understanding, cognitive function and movements.
- Showed significant reduction in aggressive behavior in elderly AD patients
- Promoted sleep to reduce anxiety in such patients.
- Olfactory dysfunction in aging may be an issue with this mode of therapy however it might be possible that the effect requires absorption into the circulatory system and not olfactory nerve terminals.

Aromatherapy with relaxation, sleep , relief of pain and reduction of depressive symptoms in dementia.

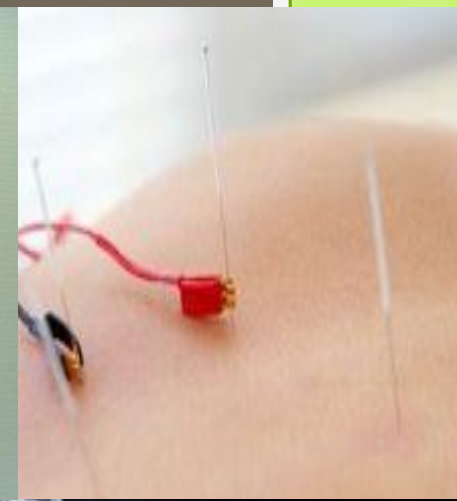
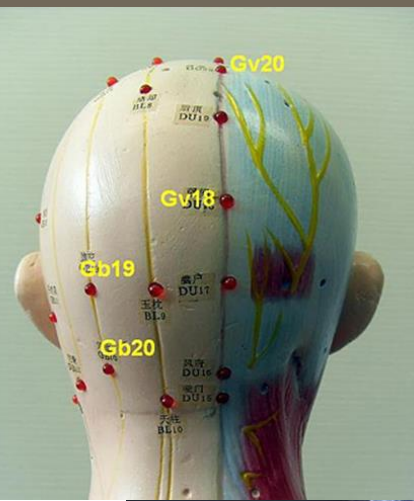
Lene Thorgrimsen Forrester¹, Nicola Maayan², Martin Orrell³, Aimee E Spector⁴, Louise D Buchan⁵, Karla Soares-Weiser^{2,*}

Editorial Group: [Cochrane Dementia and Cognitive Improvement Group](#)

Published Online: 25 FEB 2014

- Aromatherapy is the use of pure essential oils from fragrant plants
- Of RCTs (428 participants) that we found, only two trials including 186 people had useable data
- inconsistent effects of aromatherapy on measures of agitation, behavioral symptoms and quality of life
- More large-scale randomized controlled trials are needed before firm conclusions can be reached about the effectiveness of aromatherapy for dementia.
- The benefits of aromatherapy for people with dementia are equivocal from the seven trials included in this review. It is important to note there were several methodological difficulties with the included studies. More well-designed, large-scale randomized controlled trials are needed before clear conclusions can be drawn regarding the effectiveness of aromatherapy for dementia.

Acupuncture



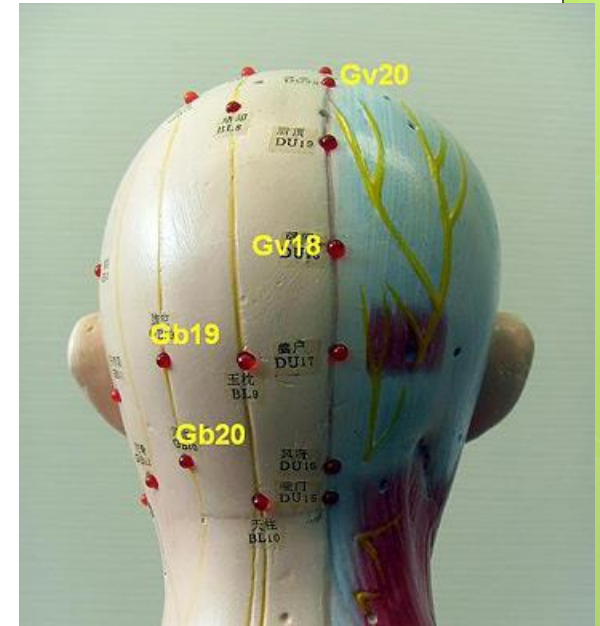
- Electro acupuncture : Uses mild electric current passing through acupuncture needles have neuroprotective effects in the learning and memory centers of the brain that might prevent senile dementia (82).
- Moxibustion. Incorporating heat therapy in the form of a burning heated stick that is generally kept close to the body without touching the skin surface.
 - Rat models, moxibustion therapy with acupuncture shows significant reduction in the neural death rate and reduced neural edema with improved learning and memory (84)
- Combination of moxibustion with acupuncture increases MMSE scores and improved the cognitive function of AD individuals in one study (76).



Aroma Acupressure

○ Points

- Beihui GV 20
- Fengchi (GB 20)
- Shenmen (HT 7)
- Neuguan (PC 6)
- Sanyinjiao (SP 6)



- Above points used in in aroma acupressure and the acupressure point with this study
- Each point was pressed for 2 minutes
- Used Lavender oil 2.5% in the aroma-acupressure group

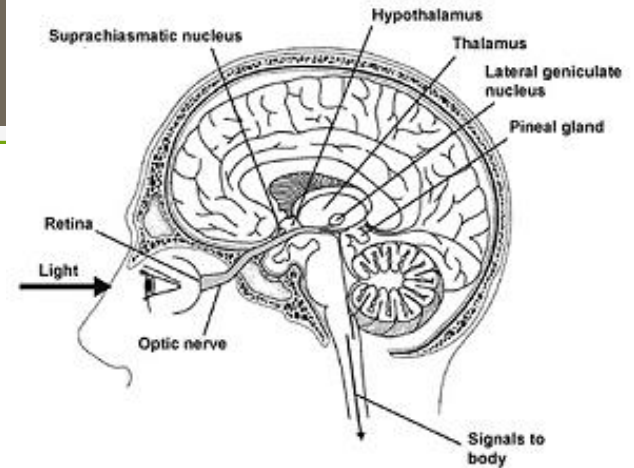
Comparison of aroma-acupressure and aromatherapy for the treatment of dementia associated agitation.

3 groups in a one month intervention

56 pts Aroma acupressure 85 years old	73 pts Aromatherapy 83 years old	57 pts control 81 years old
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- Measured agitations via : Cohen Mansfield **Agitation** Inventory scale (CMAI) scale and the heart rate variability index (HRV) index.
- CMAI scores were significantly ↓ in aroma acupressure and aromatherapy groups compared vs. control group in post testing
- Aroma acupressure had a greater effect than aromatherapy on agitation in patients with dementia however agitation was improved in both of the groups.
- Sympathetic nervous activity was lower in week four in the aroma acupressure group and in the 2nd week in the aromatherapy group.
- Future studies should continue to assess the benefits on this non-pharmacological strategies.

Light therapy



- Normal aging is usually accompanied by a decline in sleep quality and deterioration of the circadian rhythm.
- Sleep fragmentation as a result of changes in the sleep cycle that impairs cognitive performance is a common finding in AD individuals (100).
- Decreased exposure to bright light declines sleep quality while exposure to bright light may better consolidates sleep during night (101).
- SCN= suprachiasmatic nucleus = master clock, found in that hypothalamus regulates the circadian rhythm.
 - Light leads to changes in the firing rates of the neurons in the SCN that in turn affect the circadian rhythms. In dementia most triggers are reduced because diminished social contacts, eye deficiencies, less light exposure → precipitous cognitive dysfunction, behavior disturbance : agitation and sun-downing, functional impairment and depression.

Light therapy for improving cognition, activities of daily living, sleep , challenging behavior, and psychiatric disturbances in dementia :

Dorothy Forbes^{1,*}, Catherine M Blake², Emily J Thiessen¹, Shelley Peacock³, Pamela Hawranik⁴ Editorial Group: [Cochrane Dementia and Cognitive Improvement Group](#) Published Online: 26 FEB 2014

- Primary outcomes
 - Cognition
 - ADLs
 - Sleep wake disturbances
 - Challenging behaviour
 - Psychiatric disturbances
 - Adverse effects.

Modes of light therapy



- Eye level, 1 meter from the participant.
- Light therapy range from 2500 to 10000 lux either in morning or evening for one to 2 hours for 10 days to 2 months.
- Control groups received dim red light or dim low frequency blinking light at less than 300 lux.

Light intervention

- Use of bright light
- With dim red light or
- Dim low frequency blinking light at less than 300 lux

- Form of ceiling mount, light box, visor

- When : morning, afternoon, evening
- Duration < 2 hours or > 2 hours
- Strength of light therapy <2500 lux or >2500 lux

Cochrane: 11 trials

- 399 participants in the pooled studies.
- Most were older persons with AD, most frequently using a light box.
- ONE review demonstrated that light therapy had a positive effect on one outcome of interest, **Activities of daily living**.
- Pooled data resulted in significant decrease in the number of **night time awakenings**.
- No significant evidence found that light therapy decreased the decline in **cognition, shortened sleep latency time, increased sleep duration and efficacy, decreased night time activity counts, decreased challenging behaviors, or improved psychiatric symptoms including depression**. Of the 4 studies that examined **agitation**, the light therapy was not effective when administering morning, afternoon evening or all day at from 10 days to 10 weeks with the treatment lasting up to 2 years.
- Limitation Insufficient trials to be conduct subgroup analysis that would determine which modality of light therapy, what time of day, intensity and duration is most beneficial for specific types and severities of dementia.

Sun downing

- A phenomenon seen in AD characterized by a cluster of behavioral patterns including increased anxiety, confusion and some degree of aggression which is seen during the late day and at night, when the lighting outside is low.
- Sun downing results in shorter sleep latency and increased sleep duration in patients with AD
- Light therapy in AD individuals who have sun downing and sleep disturbances improved ratings of sleep wakefulness.
- Sleep disturbance and night time activity levels were minimized after a 2 hour treatment of a week (104).

Doll therapy



Massage therapy



Art Therapy



Animal Assisted Therapy

- no RCTs evaluating the effectiveness or harm of pet therapy.
- 9 non-randomized studies demonstrated decrease in :
 - Agitation and disrupted behaviors
 - Increase in social and verbal interactions
 - Increase in nutritional intake

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New Hope: Alzheimer's Disease



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FEBRUARY 25, 2016

Insulin Nasal Spray^{1,2}

MOA: Activates neuronal insulin receptors, inducing dendritic sprouting, neuronal stem cell activation, and general cell growth. Repair and regulates GS-kinase 3b.

Dosing: 20 IU to 40 IU intranasally daily

Efficacy: Some improvements in memory. However, they were short term studies (some data showing benefits up to four months).

Side Effects: none reported

Comments: Apolipoprotein E ϵ 4 carriers had lesser benefit than non-carriers in some studies.

Anti-amyloid Treatments

- Bapineuzumab
- Solanezumab
- Gantenerumab
- Crenezumab
- Aducanumab

Bapineuzumab^{3,4}

MOA: Binds N-terminal of Amyloid β -peptide and facilitates its clearance via microglial phagocytosis and cytokine release.

Dosing: 0.5 mg/kg to 1.5 mg/kg intravenous every 13 weeks

Efficacy: Antibody shown to bind to amyloid plaques and lower plaque burden. Also shown to improve measures of synaptotoxicity, and improve performance on mouse behavioral assays. However, overall human studies found no significant benefit vs placebo.

Side Effects: Inflammatory response leading to subacute meningoencephalitis. Higher rate in those with APOE ϵ 4 allele number

Solanezumab^{5,6}

MOA: Binds to the central domain of amyloid-beta, slowing down deposition

Dosing: 400 mg intravenously every 4 weeks

Efficacy: No significant difference in primary outcomes (ADAS-cog, ADCS-ADL) in studies. Follow-up study in mild Alzheimer patients appeared to slow cognitive decline by 30%

Side Effects: Incidence of amyloid-related imaging abnormalities were 0.9% with solanezumab and 0.4% with placebo for edema ($P=0.27$) and 4.9% and 5.6%, respectively, for hemorrhage ($P=0.49$).

Gantenerumab³

MOA: Binds N-terminal *and* central regions of amyloid β -peptide and facilitates its clearance via microglial phagocytosis and cytokine release.

Dosing: 105 or 225 mg subcutaneously monthly

Efficacy: Limited efficacy because of side effect profile and inferior plaque binding.

Side Effects: Inflammatory response leading to subacute meningoencephalitis

Crenezumab³

MOA: Binds N-terminal of Amyloid β -peptide and facilitates its clearance via microglial phagocytosis and cytokine release.

Dosing: 300 mg subcutaneous every other week or (15 mg/kg) intravenous every 4 weeks

Efficacy: Limited efficacy in human studies because of neuroinflammation and reduced affinity to bind immobilized plaque.

Side Effects: Inflammatory response leading to subacute meningoencephalitis



What Hope?⁶

- The negative results of these phase 3 trials may be interpreted in two ways:
 - Treatment was too late in the course of the disease (even if patients were mild-moderate)
 - Amyloid-beta ($A\beta$) alone is the wrong target for an effective treatment
- Some data on secondary analysis stating solanezumab had benefits in mild. Follow-up study ongoing in very mild or asymptomatic patients with biomarkers for Alzheimer's.
- Aducanumab has shown some promise
- Next step: re-evaluating anti-amyloid vaccine to stimulate the body's own immune defenses

Etanercept⁷

MOA: Binds tumor necrosis factor (TNF) and blocks its interaction with cell surface receptors

Dosing: 50 mg subcutaneous every week

Efficacy: No statistical significance in any of the psychometric tests (MMSE, ADAS-cog, BADLS, NPI, Cornell, CGI-I)

Side Effects: Overall well-tolerated; however, infections, injection site reactions, respiratory tract infections occurred in a small sample size.

Coconut Oil⁸

Potential MOA: Medium-chain fatty acids are easily converted to ketones which may be beneficial in memory impairment as an energy source. Cytokinins may also prevent aggregation of amyloid beta peptides.

Dosing: 1.25 oz serving twice daily

Efficacy: May have short term benefits. Study currently recruiting participants

Side Effects: Increase weight, cholesterol, LDL concentrations?

Omega-3 fatty acid (DHA) plus bexarotene⁹

MOA: Bexarotene is an agonist of certain nuclear receptors which act to ameliorate AD-related cognitive impairment and amyloid accumulation in murine models of AD. DHA also reduces inflammatory markers in mice.

Dosing: N/A

Efficacy: Restores working memory in mice. Single agents or in combination reduce inflammation in vivo, reduce cortical, dense-core plaques in vivo, and promote gene expression, lipidation of ApoE, and reduce soluble amyloid-beta levels in vivo.

Side Effects: Bexarotene: hypertriglyceridemia; DHA is used to prevent and/or reduce the elevated triglycerides.



Antidepressant Use in Dementia

Selective Serotonin Reuptake Inhibitors

Paroxetine

Fluoxetine

Citalopram

Escitalopram

Sertraline



Selective Serotonin Reuptake Inhibitors¹⁰⁻¹⁶

Drug	Dose (mg/day)	Comments
Citalopram	10-40	May decrease agitation; *30-40 mg/day show cognitive and cardiac adverse effects (e.g., increase QT interval, bradycardia)
Escitalopram	5-20	May be less sedating than citalopram?
Sertraline	25-150	More activating; may have more diarrhea
Paroxetine	10-40	More sedating; watch drug-drug interactions
Fluoxetine	20-40	More activating; long half-life; watch drug-drug interactions

What about other antidepressants?

(or other options)



Other Antidepressants¹⁷⁻²¹

Drug	Dose (mg/day)	Comments
Venlafaxine	25 up to a target dose of 150 – 225	Dry mouth, constipation, dizziness
Desvenlafaxine	50	Lack of literature
Duloxetine	20-30 up to a target dose of 60	Dry mouth, constipation, dizziness, may see agitation. May be more difficult to taper. Watch protein binding
Bupropion	75-150	Nervousness, insomnia, increase seizures. SR may be preferred for geriatrics
Mirtazapine	7.5-40	Used to stimulate appetite/increase body weight. Sedating at lower doses. About 2 kg increase after 3 months. Recent data showed minimal effects on sleep in Alzheimer’s disease
Trazodone	50 for Alzheimer’s (< 200 for elderly)	For sleep not depression

Managing Psychosis



MEDICATIONS USED²²

Antipsychotics:

High incidence of adverse cardiovascular effects and high risk of death.

Second generation (atypical) better than first generation (conventional or typical) based on efficacy and safety profile. However, they are not approved by FDA.

Risperidone is one of the most studied agents.

Antipsychotics

Quetiapine

Olanzapine

Long Acting IM Formulations

Risperidone

Aripiprazole



Antipsychotics²²⁻²⁵

Drug	Dose (mg/day)	Comments
Risperidone	0.5-1.5	EPS, Risk for cerebrovascular events, orthostatic hypotension
Aripiprazole	7.5-12.5	Sedation at higher doses. No increased cardiovascular outcomes, cerebrovascular accidents, increased appetite or weight gain demonstrated in meta-analyses.
Olanzapine	5-7.5	Sedation, weight gain, orthostatic hypotension, cerebrovascular accidents
Quetiapine	50-200	Sedation, orthostatic hypotension. (NOT TO BE USED FOR SLEEP)
Ziprasidone	60-80	QTc prolongation
Haloperidol	0.5-3	EPS, tardive dyskinesia

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