NICM
Health Research Institute

INTEGRATIVE MEDICINE FOR MENTAL HEALTH AND NEUROCOGNITION

A therapeutic outline

This therapeutic outline provides an introduction to a variety of integrative medicine therapies that have been used and researched in the management of mental health and neurocognitive disorders. This includes treatments with either nutraceuticals[1] or herbal medicine monotherapies[2] or where these are used adjunctively with conventional medical treatments. Mind-body, manual, lifestyle and other traditional therapies are also reviewed.

The outline has been drafted by experts in the field. However it is not meant to be an exhaustive review of scientific evidence, such as a systematic review or meta-analysis, which is not its purpose. This outline provides a description of the therapy and a brief narrative review of the emerging evidence considered by the researchers at NICM Health Research Institute to be important science being undertaken in the area of integrative medicine for mental health and neurocognition.

Why people use integrative medicine for mental health and neurocognition

Mental health conditions account for about one-third of the world's disability due to all health problems in adults.(1) Further, mental illness and substance abuse are in the top five groups causing the greatest burden in Australia.(2) Neurocognitive disorders also contribute significantly to disease burden in Australia. For example, dementia is recognised as a serious and growing health problem in Australia and numerous other countries with an ageing population. Dementia is the leading cause of disability among people aged 65 years and over in Australia.(3) Furthermore, assessment of cause of death data for Australia for 2018 found that dementia, including Alzheimer's disease, remained the second leading cause of death after ischaemic heart disease that year (noting that dementia was the leading cause of death in women).(4) Internationally, it is estimated there are over 50 million people living with dementia and that spending on dementia will in time outstrip spending on any other health condition, currently costing $818 billion USD worldwide.(5)

Little data have been collected on the prevalence of use of integrative medicine by people living with dementia or experiencing mental illness (in particular mood disorders). A study completed in Norway on the use of dietary supplements among people with dementia presenting to a memory clinic found that 46 per cent of the sample (of 151 people) used dietary supplements.(6) A nationally representative sample in the United States of America of 2055 people interviewed during 1997–1998 also revealed that 54 per cent of those with severe depression reported using integrative medicine during the previous 12-months.(7)

[1] Nutraceuticals are nutrient-based natural products which are produced via pharmaceutical good manufacturing practice, standardised and optimised.
[2] A monotherapy describes a treatment that has only a single active ingredient. The single active ingredient could be a medicine or a vitamin or a single herbal ingredient.

Australia has one of the highest rates of consumption of complementary medicine (CM) per capita in developed countries,(8) with more money being spent on CM than prescription drugs.(9) It is estimated that two out of three Australians use CM, and further to this, 42 per cent do so to manage or prevent chronic diseases such as dementia.(10)

Key interventions under the umbrella of integrative medicine include - lifestyle medicine (e.g. Physical activity/exercise or dietary modification), nutraceuticals (regarded as pharmaceutical grade nutrients), herbal medicines, and CM therapies such as yoga, tai chi or massage.

Effectiveness of integrative medicine for mental health

The following evidence summary provides an overview of potential clinical areas of benefit.

Nutraceuticals and herbal medicines for mental health

Depression - Treatment with nutraceuticals and herbal medicine monotherapies

- *S-adenosyl-L-methionine (SAMe)*[3] – There is mixed evidence on the efficacy of SAMe as a monotherapy for the treatment of depression. Older meta-analyses (MAs)[4] concluded SAMe is effective for treating depression with an efficacy superior to placebo and equivalent to the conventional antidepressants,(11, 12) but a more recent Cochrane review did not demonstrate superior efficacy of SAMe as a monotherapy in comparison with placebo.(13) A randomised clinical trial (RCT) which initially found a very strong placebo response, on reanalysis showed that SAMe was more effective than placebo in males but not in females.(14, 15) Finally, an 8-week double-blind RCT testing 800mg/day of SAMe monotherapy versus placebo in 49 participants with major depressive disorder (MDD) not taking antidepressants found a non-significant effect in favour of SAMe. Subgroup analyses revealed a marginally significant treatment effect in those with milder depression, while no benefit was noted in those with more severe depression.(16) More research comparing the efficacy of SAMe with newer generations of antidepressants is needed as well as research to determine if there are gender-specific differences in response.(15) Furthermore, the effect of SAMe treatment in those with milder versus more severe depression warrants further investigation.(16)

- *St John's Wort (Hypericum perforatum)* - The available evidence suggests that standardised extracts of St John's Wort are superior to placebo in patients with mild to moderate or major depression and are similarly effective as standard antidepressants. Further to this, St John's

[3] S-adenosyl-L-methionine (SAMe) is a compound found naturally in the body. SAMe helps produce and regulate hormones and maintain cell membranes; and is involved in the one-carbon cycle which generates a range of neurochemicals.
[4] A meta-analysis (MA) is a statistical analysis that is used to combine the results of multiple scientific studies. This included must studies address the same research question. Typically, randomised controlled trials are included in MAs.

Wort has fewer side effects than standard antidepressants.[5](17, 18) While commonly now only recommended for mild to moderate depression due to clinical concerns about using it in patients with more severe MDD, St John's Wort is safe for use in patients with MDD as long as these individuals are closely monitored and can be placed on standard medications if needed.(19) Standardised pharmaceutical grade St John's Wort is recommended in all instances rather than non-standardised formulations.

  - *NOTE* - There is little evidence on the efficacy and safety of St John's Wort in treating adolescent with MDD.(19)

- *Tryptophan and 5-Hydroxytryptophan* – There is some human clinical trial evidence suggesting tryptophan and 5-hydroxytryptophan are better than placebo at alleviating depression, however most trials are of poor quality.(20) While this is the case, there is a significant body of research showing an association between tryptophan metabolism dysfunction and depression and suicide, noting that tryptophan is the precursor amino acid for serotonin and melatonin. Acute Tryptophan Depletion (ATD) trials, which result in a dramatic decrease in plasma tryptophan concentrations, have repeatedly shown a lowering of mood scores in a proportion of individuals with depression or a history of depression(21-25) with relatively few health controls exhibiting mood lowering effects in response to ATD (and those who do show a lesser degree or reported negative mood).(26) Administration of tryptophan enriched cereals at breakfast and dinner to elderly people who suffered from sleep onset and sleep consolidation problems improved mood, sleep and antioxidant capacity.(27) Finally, there is growing awareness that mood and sleep disorders are impacted by immune system response which will inform research in this area moving forward.(28)

- *Inositol* - There is no good evidence that inositol is of benefit in the treatment of depression.(29, 30)

- *Saffron (Crocus sativus)* – There is high-quality evidence that saffron is as effective as antidepressant medications (and more effective than placebo) in the treatment of depression.(31, 32) As most of the RCTs to date have been done in Iran, studies completed in other jurisdictions are required. Furthermore, the cost of saffron may be prohibitive.

- *Turmeric (curcumin)*[6] – There is evidence from a recent systematic review with meta-analysis(33) and a systematic review(34) that curcumin containing nutraceuticals administered as monotherapies for 4-8 weeks may be effective in depressed patients. The meta-analysis included six clinical trials and found the pooled standardised mean difference from baseline Hamilton Rating Scale for Depression scores supported the significant clinical efficacy of curcumin in ameliorating depressive symptoms.(33)

[5] It is worth noting that findings were more favourable to St John's Wort extracts in studies form German-speaking countries where these products have a long tradition and are often prescribed by physicians, while in studies from other countries St John's Wort extracts seemed less effective.

[6] Turmeric is a flowering plant of the ginger family and the roots – also known as rhizomes – are used in cooking. A key active ingredient in turmeric is curcumin, which is one of a class of chemicals known as curcumoids. Curcuminoids are a mixture of hydrophobic polyphenolic compounds and aside from curcumin, the most widely studied curcuminoid, two other curcuminoids found in turmeric are dimethoxy curcumin and bisdemethoxycurcumin.

- *Roseroot (Rhodiola rosea)* – There is mixed evidence that roseroot is effective in improving mood in people with depression.(35-38)

- *Omega-3 fatty acids* – There is weak evidence of a small positive effect from high-dose eicosapentaenoic acid (EPA) omega-3 formulas used as a monotherapy in clinical depression.(39)

Depression - Adjunctive treatment of mainstream medical treatments with nutraceuticals and herbal medicines

- *Eicosapentaenoic Acid rich omega-3 fatty acids (EPA)* - There is strong evidence that augmentation[7] of antidepressant medication with EPA-rich omega-3 fatty acids significantly reduces depressive symptoms when compared to use of antidepressant medication alone for the treatment of MDD, noting the effect is not seen in patients with depression as a comorbidity to chronic physical conditions.(39)

- *Methylfolate or folinic acid* - There is modest evidence that augmentation of antidepressant medication with methylfolate or folinic acid – the active forms of folic acid - has an impact on depressive symptoms when compared to the use of antidepressant medication alone. Folic acid itself however cannot be recommended as a treatment for depression.(40-49)

- *S-adenosylmethionine (SAMe)* – A number of small open-label trials found that adjunctive use of SAMe further reduced depressive symptoms in people on antidepressant medication,(50-52) and an open-label trial and an RCT concluded that SAMe has efficacy as an augmentation agent in partial and non-responders to selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitor.(50, 53) However, a recently published double-blind RCT examining the effect of adjunctive SAMe in treating non-remittent MDD in 107 outpatients concluded that 800mg/day of SAMe (given for 8-weeks) is not an effective adjunctive treatment in MDD, and no obvious biomarker[8] reflected any differential response to treatment.(54)

- *Vitamin D* - There is limited evidence that adjunctive use of Vitamin D (D3 form) with antidepressant medication reduces depressive symptoms.(39, 55, 56)

- *Zinc* - There is emerging evidence that augmentation of antidepressant medication with a zinc supplement is more effective at lowering depressive symptoms of depressed individuals when compared to antidepressant medication alone, in particular in individuals previously resistant to antidepressant treatment.(57, 58)

- *Turmeric (curcumin)* - A meta-analysis published in 2016 of six clinical trials (five RCTs; one open-label controlled trial) found that people with MDD treated with antidepressants and

[7] Augmentation is the administration of an additional pharmacotherapy to enhance the efficacy of the existing intervention.
[8] Differential response to SAMe was not modified by a range of key genotypes (e.g. COMT), nor reflected in a change of homocysteine, red cell folate, or brain-derived neurotrophic factor.

curcumin containing nutraceuticals had significantly higher reduction in depression symptoms than those treated with antidepressant therapy alone). The authors found curcumin had the highest effect when given to middle-aged patients, for longer duration of administration, and at higher doses.(59)

- *Saffron (Crocus sativus)* – The existing evidence suggests a potential for saffron to be an efficacious adjunctive to antidepressants for treatment of depression. A meta-analysis of RCTs published by Marx and colleagues in 2019 investigated the effect of saffron supplementation, as both an adjunctive therapy and monotherapy, on symptoms of depression and anxiety in clinical and general populations compared with pharmacotherapy or placebo. Adjuvant supplementation of saffron in people taking antidepressants was found to be efficacious (and the effect size was large), but the authors note the studies included in the meta-analysis were of relatively short duration and of limited sample size and the vast majority of studies had been completed in Iran.(60)

Anxiety disorders - Treatment with herbal medicines as monotherapies

- *Passionflower (Passiflora incarnata)* – There is emerging evidence from relatively few small trials that passionflower is effective in the treatment of anxiety, including being as effective as standard pharmaceutical comparators used for the treatment of anxiety disorders.(61, 62)

- *Gingko biloba* - The research into the cognitive anxiolytic effects of *Gingko biloba* is inconsistent and therefore *Gingko biloba* cannot be recommended to individuals with anxiety disorders.(63) There is, however, evidence from a single double-blind RCT that ginkgo is effective in treatment of generalised anxiety disorder (GAD).(64) The trial used the EGb 761 extract (480 or 240 mg per day) or placebo for 4 weeks in adults with GAD (n=82), as well as patients with adjustment disorder with anxious mood (n=25), as assessed via the Diagnostic and Statistical Manual of Mental Disorders (Third edition Revised). At the end of the trial participants' Hamilton Anxiety Rating Scale (HAM-A) total scores decreased significantly in both the 480 mg per day and 240 mg per day ginkgo groups, relative to placebo, in a dose-dependent manner. Changes were significantly different from placebo for both treatment groups with high-dose group and p=0.01 low-dose.

- *Lemon balm (Melissa officinalis)* - There are some promising findings on the efficacy of lemon balm as a cognitive anxiolytic from a RCT involving 18 healthy adults (65) and an RCT involving 20 people suffering from mild to moderate anxiety disorders.(66) Lemon balm was administered as a one-off acute dose in the case of the healthy adults and was administered on a daily basis for 15-days - a chronic dose - in the case of the RCT with people suffering from mild to moderate anxiety disorders. Larger trials are needed to confirm these findings including efficacy in the longer term. (See also the section below on neurocognitive disorders)

- *Bioactive constituents of tea (polyphenols, amino acids and caffeine)* - The primary bioactive constituents of tea – polyphenols such as epigallocatechin gallate, amino acids such as L-theanine, and caffeine - have been studied in isolation and in combination to determine effects on cognition and anxiety, with studies showing the active constituents of tea have cognitive

anxiolytic properties, particularly when administered in combination. Studies assessing bioactive constituents of tea as monotherapies, that is without being used with other medications) have been completed in healthy populations.(67-76) Further work is needed to elucidate the mechanisms underpinning these combined/synergistic effects.

- *Sage* - Preliminary findings suggest oral administration of sage (particularly *S. officinalis or S. lavandulaefolia)* is a cognitive enhancer in individuals with Alzheimer's disease and an anxiolytic in healthy, non-clinical individuals.(77-83) Most research to date has assessed the efficacy of an acute dose of sage on key outcomes, with the exception of the trial completed by Akhondzedah and colleagues where the intervention dose of sage was fixed at 60 drops per day for a 4-month period.(83) A key point is that no studies to date have investigated the effects of sage as a cognitive anxiolytic in individuals with a clinical anxiety disorder.

- *Rosemary officinalis* - Preliminary findings suggest promising effects of rosemary aromatherapy (via massage or inhalation) as an anxiolytic in both healthy individuals and those experiencing clinical levels of anxiety.(84-86) Furthermore, there is support for rosemary as a cognitive enhancer.(87-89)

- *Kava (Piper methysticum)* - Compared with placebo, kava extract is an effective treatment for symptomatic anxiety; the data available from the reviewed studies suggest that kava is relatively safe for short-term treatment. However, the evidence on the effectiveness of kava for treatment of GAD is mixed, and a recent RCT showed it to not be more effective than placebo.(90-94) There is insufficient evidence currently on the efficacy of kava compared with synthetic agents such as benzodiazepines or antidepressants.(19)

- *Galphimia (Galphimia glauca)* – There is emerging evidence that galphimia has an anxiolytic effect and is as effective as lorazepam for the treatment of anxiety. A 4-week double-blind RCT comparing the therapeutic effectiveness of an aqueous extract of galphimia with lorazepam in patients with GAD found no significant difference between groups in the anxiolytic effect across time.(95) While this was the case, no significant side effects were noted in the galphimia group, whereas 21 per cent of people in the lorazepam group experienced excessive sedation. A follow-up study found a significantly greater reduction in anxiety occurred - as measured using the Hamilton Anxiety Rating scale - for galphimia treatment in comparison with lorazepam over the course of the clinical trial (15-weeks). There was no statistical difference in therapeutic safety between the two arms of the trail(96). Placebo controlled trials are needed in this space.

- *Chamomile (Matricaria recutita)* – There is mixed evidence that supplemental chamomile is effective in treating GAD.(97-99)

- *Ashwagandha (Withania somnifera)* – There is emerging evidence that ashwagandha is effective in treating anxiety- and/or stress-related outcomes,(100, 101) including in people with GAD.(102)

Anxiety disorders - Adjunctive treatment of mainstream medical treatments with nutraceuticals

- *L-theanine*[9] - While L-theanine may be an efficacious treatment option in sub-clinical anxiety or anxiety which is secondary to other conditions (such as MDD or schizophrenia/ schizoaffective disorder),(103) evidence suggests no effectiveness of L-theanine as an adjunctive treatment to further reduce anxiety in individuals on stable antidepressant treatment for GAD.(104) However, there has been limited research to date in clinical populations.(103)

Bipolar disorder – Adjunctive treatment of mainstream medical treatments with nutraceuticals and herbal medicines

- *Omega-3 fatty acids* – Omega-3 fatty acids, specifically EPA used alone or in combination with docosahexaenoic acid (DHA) (but with a higher EPA-to-DHA ratio), may be an effective adjuvant in combination with mood stabilisers in the depressive phase of bipolar illness, but do not significantly improve symptoms of mania or rapid cycling.(105-107) A meta-analysis published in 2012 which included five placebo controlled RCTs concluded that omega-3 supplementation (EPA alone or EPA combined with DHA) of conventional mood stabilisers significantly reduced depressive symptoms in people with bipolar disorder when compared to the control intervention measured using a variety of different scales. (107)

- *NAC* – Recent meta-analyses have concluded that adjunctive treatment of standard medications with NAC for individuals with bipolar disorder is not effective:(39) there was no effect on overall illness severity, mania ratings(108) or depressive symptoms(109) in this cohort.

- *Choline*[10] *or Phosphatidylcholine*[11] - While there is emerging evidence that choline or phosphatidylcholine supplementation used adjunctively to standard medications may reduce the severity of mania and depressed mood in bipolar patients, this evidence is limited.(106) To date one RCT and one open-label pilot of lithium-treated patients with rapid cycling bipolar disorder have been completed: the RCT (n=8) showed no effect on mood outcomes(110) and the open-label trial (n=6) showed a positive effect on symptoms of mania and depression in the majority of particulars.(111)

- *Chromium* – Only one trial of chromium use in bipolar disorder has been published and this trial evaluated open-label adjunctive chromium for treatment-resistant, rapid-cycling bi-polar disorder (n = 30) over the course of two-years. Approximately one-third of patients

[9] L-theanine is an amino acid derived almost exclusively from tea leaves (*Camellia sinensis*), with the highest concentrations in green, oolong and Pu-erh teas.
[10] Choline is a water-soluble vitamin-like nutrient available through the diet and also produced in the human body. Choline and its metabolites play important roles in the structural integrity and signalling of cell membranes, cholinergic neurotransmission (which has anti-excitatory effects), as well as being a source for methyl groups via its metabolite, trimethylglycine (betaine). Choline administration has been reported to increase brain phosphatidylcholine levels. Choline is a necessary precursor for synthesis of acetylcholine. Abnormally low levels of acetylcholine in the central nervous system may underlie some cases of mania.
[11] Phosphatidylcholines - a class of phospholipids that incorporate choline as a headgroup - are a major constituent of cell membranes.

experienced a reduction in depressive symptoms; however, participant drop-out rates were high (with only seven participants able to be followed up at one-year and the mean time to discontinuation of supplementation calculated at 204 days). The long-term benefit of chromium for the treatment of bipolar disorder is not confirmed, but does warrant further investigation, particularly its tolerability given the high attrition rates.(112)

First episode psychosis[12] - Adjunctive treatment of mainstream treatments with nutraceuticals

- *Omega-3 fatty acids* - evidence for the effectiveness of adjunctive supplementation with omega-3 fatty acids in people suffering first-episode psychosis (FEP) in ameliorating symptoms and improving real-world function is equivocal, but emerging evidence suggests that longer term supplementation with omega-3 fatty acids – 24-weeks versus 12-weeks - is effective in improving symptoms[13] and real-world function.(113-118)
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- *Amino acid supplementation* – there is emerging evidence that supplementation with the amino acid taurine as an adjunctive to usual medication significantly improves total symptoms, psychotic symptoms, depression and functioning in people with FEP.(119)

- *Vitamin C supplementation* – supplementation with vitamin C as an adjunctive treatment to usual medical regimes has been shown to improve oxidative status in FEP, in association with reduced total symptoms.(120)

Schizophrenia - Adjunctive treatment of mainstream treatments with nutraceuticals

- *Vitamin B* - There is limited evidence that vitamin B interventions using higher dosages or combining several vitamins used as an adjunct to usual medication regimes are effective in reducing psychiatric symptoms in individuals with schizophrenia.[14](46, 121-126). Evidence does suggest, however, that providing these supplements early on in the illness may be most beneficial as duration of illness has been shown to be negatively correlated with treatment effectiveness.(127) More recent data indicates that the beneficial pooled effects of b-vitamin supplementation are driven by large, positive effects in early trials of high-dose methylfolate as an adjunctive treatment for schizophrenia.

[12] First-episode psychosis (FEP) refers to the first two to five years of a psychotic disorder, such as schizophrenia.
[13] The symptoms people with schizophrenia and psychosis experience are described as positive, negative, general and total. Positive symptoms are psychotic symptoms and examples are hearing voices and paranoia. Negative symptoms include symptoms such as social withdrawal, apathy, and lack of emotion. General symptoms include depression, anxiety, and physical symptoms. Total symptoms describe all symptoms including positive symptoms, negative symptoms and general symptoms.
[14] Genotypes affecting metabolism of vitamins, such as those impacting folate metabolism, will likely impact a particular individual's response to vitamin therapy.

- *Vitamin E* – While there is no evidence that Vitamin E supplementation improves tardive dyskinesia[15] associated with antipsychotic medications, it appears supplementation with Vitamin E significantly reduces the risk tardive dyskinesia 'worsening' over a year, although the quality of the trials completed to date in this space has been low.(128)

- *Ginkgo biloba* – There is emerging evidence that gingko biloba used as an adjuvant to antipsychotics is more effective than antipsychotic medication alone in ameliorating total and negative symptoms of chronic schizophrenia; this is potentially due to the antioxidant effects. However, these effects have only so far been observed in studies based in China, and yet to be replicated in Western settings. No significant between-group adverse effects were revealed. However, a reduction of extrapyramidal side effects[16] was not evident across the ginkgo cohort.(129, 130)

- *N-acetylcysteine (NAC)* – There is emerging evidence that adjunctive use of NAC is more effective in treatment of schizophrenia than treatment with standard pharmaceutical medications alone;(39, 130-133) in particular the 'negative' symptoms of the condition.

- *Glycine* - There is evidence that adjunctive use of glycine with standard antipsychotic medication excluding clozapine Is effective in improving negative symptoms in people with schizophrenia.(134-141)

- *Sarcosine*[17] – There is emerging evidence that sarcosine used as an adjunctive with antipsychotic medication aside from clozapine has positive effects on total symptom scores in people with schizophrenia.(39, 142, 143)

Obsessive compulsive disorders - Treatment with nutraceuticals and herbal medicine monotherapies

- *N-acetyl cysteine (NAC)* – Only a limited number of RCTs have investigated the use of NAC as a monotherapy for the treatment of OCD and obsessive-compulsive related disorders[18] to date; aside from RCTS, there are a number of published case reports. Findings are mixed which raises the possibility that NAC may be effective only in a subset of OCD patients. Furthermore, future research involving NAC for OCD may require larger samples to detect moderate or small effect sizes, involve dosage or formulation differences, use in concert with exposure therapy, or an additional post-study observational period to mitigate study withdrawal.(144, 145)

[15] **Tardive dyskinesia** is a side effect of antipsychotic medications used to treat schizophrenia. It is a neurological disorder that causes stiff jerky movements of a person's face or body which cannot be controlled and so are involuntary. Examples include twitching, grimacing, and thrusting.
[16] **Extrapyramidal side effects:** Physical symptoms, including tremor, slurred speech, akathesia, dystonia, anxiety, distress, paranoia, and bradyphrenia, that are primarily associated with improper dosing of or unusual reactions to neuroleptic (antipsychotic) medications.
[17] Sarcosine is also known as N-methylglycine and is an intermediate and by product in glycine synthesis and degradation.
[18] Obsessive compulsive related disorders are hoarding, excoriation, and trichotillomania. Excoriation is a skin picking disorder where a person cannot stop picking at their own skin, often during times of stress and anxiety. This can lead to bruising, cuts/ abrasions or bleeding. Trichotillomania is a hair-pulling disorder.

- *Milk thistle (Silybum marianum)* – There is evidence that milk thistle is as effective as the selective serotonin reuptake inhibitor fluoxetine from a single RCT (n=35 participants with Yale Brown Obsessive Compulsive Score (Y-BOCS) greater than 21) but larger placebo controlled trials are needed to confirm this finding.(146)

- *Borage (Echium amoenum)* – There is evidence from a single methodologically sound study that investigated the efficacy and safety of borage in 44 patients with diagnosed OCD in a 6-week placebo controlled, double-blind, parallel-group trial that borage recues anxiety in people with OCD as measured using the Hamilton Anxiety Rating Scale, but has little to no effect on symptoms of OCD (as measured using the Y-BOCS).(146) This anxiolytic effect is beneficial as comorbid GAD is common in sufferers of OCD.

- *Saffron (Crocus sativus)* – Little research has been completed to date to determine if saffron is effective in the treatment of OCD. A double-blind RCT comparing the efficacy of saffron to fluvoxamine in the treatment of mild to moderate OCD concluded that saffron and fluvoxamine are equally effective.(147)

- *Valerian (Valeriana officinalis L.)* – While limited research has been done in this space, a single double-blind placebo controlled trial of 31 outpatients with who met the DSM-IV-TR criteria for OCD (based on structured clinical interview) concluded valerian has some anti-obsessive and compulsive effects, but that further studies are needed to confirm these finding.(148)

- *Myo-inositol*[19] – is not effective for OCD.(39)

Obsessive compulsive disorders - Adjunctive treatment of mainstream treatments with nutraceuticals and herbal medicines

- *NAC* – The efficacy of adjunctive use of NAC with a variety of standard medications for OCD has been assessed in a number of clinical trials to date, and a systematic review of this evidence published in 2018 concluded there was evidence (approximating statistical significance) that favoured the use of NAC as an adjunct in OCD patients.).(149)

- *Ashwagandha (Withania somnifera)* – A single placebo-controlled trial assessing the efficacy of ashwagandha used adjunctively for the treatment of OCD with SSRIs including 31 patients with a confirmed diagnosis of OCD according to the DSM-IV-TR concluded ashwagandha extract may be beneficial as a safe and effective adjunct to SSRIs in the treatment of OCD.(150)

[19] Myo-inositol is a glucose isomer which has a long history of use in the treatment of psychiatric disorders.

Insomnia - Treatment with nutraceutical monotherapies

- There are currently no effective ingestive monotherapy for insomnia. The most recent systematic review and meta-analysis published in 2015,(151) which assessed the evidence base for herbal medicines as monotherapies for insomnia (14 RCTs; 1602 participants), confirmed the findings of previous reviews of no effective treatment.(152-154) The studies included all but one trial that was double-blinded and the vast majority of studies trialled orally administered valerian (n=12), with single studies testing chamomile, kava and wuling[20].

- While the evidence on valerian currently does not support its use in treating insomnia, a valerian hops extract combination appears to have a small positive effect and can be considered for mild insomnia.(155, 156)

Safety of nutraceuticals and herbal medicines for mental health

- *Omega-3 fatty acids* -
    - It has been suggested that higher-dose omega-3 supplementation may increase bleeding, impair immune function, increase lipid peroxidation, and impair lipid and glucose metabolism, but it appears such outcomes are rare.(157)
    - There is also evidence that omega-3 likely increases LDL cholesterol concentrations, but only when dosages of DHA and combined EPA/DHA are over 2 g/day.(157)

- *Folic acid* - While meta-analyses have not revealed definitive evidence for the association between folic acid supplementation and a range of cancers,(158) and adequate folate consumption from vegetables and whole grains has potential cancer-protective properties, high dosages of folic acid may not be advised in people with cancer, since it increases cell proliferation.(159)

- *SAMe* - Has been associated with an increased risk of hypomania or manic switching in depressed patients. However, the switching has primarily been reported in patients with a diagnosed bipolar disorder and with intravenous or intramuscular administrations of SAMe and not observed in clinical trials of oral administration of SAMe.(160-162)

- *Vitamin D* - Hypercalcemia and vascular calcification may occur when vitamin D is used at high-doses (275 mg/day).(163)

- *St John's Wort* - Has a very sound safety profile(164) with the only caveat being potential drug interactions, including a tendency to reduce the serum levels of many pharmaceuticals.(19) However, St John's Wort formulations with low levels of hyperforin (<1%) do not show these drug interactions and still maintain antidepressant activity.(165)

[20] Wuling is a single herbal formula from *mycelia of precious Xylaria nigripes (Kl.)* used in Traditional Chinese Medicine.

- *Gingko biloba* – There are reports of gingko biloba interacting with the following classes of drugs: anticoagulants, anti-inflammatory agents, antihypertensives, and anaesthetics.(166)

- *Kava (Piper methysticum)* - Was withdrawn from European and United Kingdom markets in 2002 due to concerns over reported hepatotoxicity (liver toxicity). Therefore, use of only the peeled roots from noble cultivars (traditionally safe and therapeutic cultivated species) using a water solute extraction method is advised.(167) Herb-drug interactions have been noted with antidepressants, antiplatelets, sedatives and drugs metabolised through the cytochrome p450 class of iso-enzymes.(166) Kava is available for sale in Australia and regulated by the Therapeutic Goods Administration.

- *Reserpine* - Reserpine has relatively few and minor adverse effects when used at dosages of less than 0.2 mg/d; the main adverse effect is nasal congestion.(168) However, use of reserpine in the United States of America and other Western countries is restricted because of safety concerns that include nausea, vomiting, gastric ulceration, cramps and diarrhoea, erectile dysfunction, hypotension, and bradycardia. Western-trained psychiatrists are also cautious about reserpine because of the increased risk of depressed mood and suicide, although most reports of suicide have come from early uncontrolled studies with dosages as high as 0.5 mg/d.(169)

Mind-body therapies for mental health

- *Yoga for depression, anxiety and post-traumatic stress disorder (PTSD)* - Numerous reviews of evidence for mental health conditions have reported that while further research is generally recommended, there is growing evidence from over 30 randomised controlled trials for the effectiveness of yoga as an intervention for depression, anxiety and PTSD.(170-177)

- *Yoga for schizophrenia* – Yoga is beneficial for quality of life in people with schizophrenia.(178-180)

- *Tai chi for anxiety* - A systematic review of the research literature on tai chi for anxiety published in 2015 found 12 of the 17 studies included in the review found positive effects in outcome measures related to anxiety and concluded that tai chi is a promising modality for anxiety management.(181)

- *Tai chi for depression* - A meta-analysis of RCTs on tai chi for depression including four trials comparing tai chi with a wait list control group and a total of 253 participants found tai chi significantly reduced depression symptoms as compared to a wait list control.(182) This conclusion was supported by the finding of another systematic review and meta-analysis published the following year.(183)

- *Tai chi for stress management* - A meta-analysis including RCTs and non-randomised studies found that regular practice of tai chi positively affected stress management in both healthy individuals and individuals with chronic conditions (effect score 0.66; 95% CI, 0.23 to 1.09).

Heterogeneity of included studies was high (I^2 = 82%), but the result remained significant after the study with the largest effect was excluded.(184)

Manual therapies for mental health disorders

- *Transcranial magnetic stimulation (TMS) for bipolar disorder* – A review published in 2018 examining the efficacy of repetitive TMS in the treatment of bipolar disorder concluded there was little evidence supporting benefit over sham.(185)

- *Massage therapy for depression* – There is currently no good evidence to suggest that massage therapy (Swedish style) is an effective treatment for depression in patients with a depressive disorder or sub-syndromal symptoms of depression.(186)

Lifestyle therapies for mental health wellbeing

- *Exercise for people with major depressive disorder (MDD)* – A meta review published in 2019 examined the impact of exercise on people with MDD and other mental health disorders. Eight meta-analyses included in the meta review examined the effects of exercise in MDD. These was consistent evidence across these meta- analyses that structured moderate-to-vigorous intensity exercise can have a positive impact on symptoms of depression as an add on treatment for adolescents and adults (both working age and beyond working age).(187)

- *Exercise for people with anxiety* – A meta review assessing three meta-analyses that investigated the benefits of exercise in anxiety and stress-related disorders in adults found that exercise was more effective than control conditions in reducing anxiety symptoms.(187)

- *Exercise for people with schizophrenia* – The same meta review found exercise is an effective adjunctive treatment to standard medication regimes for people with schizophrenia, reducing positive and negative symptoms (n=2 meta- analyses included), and that exercise also improves global cognition in this cohort of individuals (n=1 meta-analysis). Emerging data suggest that higher intensities of aerobic exercise may produce.(187) While a variety of different exercise types are beneficial, it appears aerobic exercise at higher dose (90-minutes per week) is needed to benefit mental health domains (including psychiatric symptoms, functional disability and cognition), and research shows people with schizophrenia find it easier to maintain an exercise program when it is supervised and done in a group (rather than unsupervised solitary exercise).(188)

- *Exercise for children with ADHD* – Evidence from a systematic reviews and meta-analysis published in 2015 examined the evidence of effectiveness of exercise interventions on attention deficit hyperactivity disorder (ADHD)-related symptoms in children and adolescents. The authors concluded the main cumulative evidence indicates that short-term aerobic exercise, based on several aerobic intervention formats, seems to be effective for

mitigating symptoms such as attention, hyperactivity, impulsivity, anxiety, executive function and social disorders in children with ADHD.(189)

- *Smartphones to deliver mental health interventions* - There is good evidence that the use of smartphones to delivery mental health interventions is moderately effective in improving depressive symptoms in both clinical populations[21] and non-clinical populations[22]. More specifically, research shows smartphone mental health interventions are more effective in populations with mild to moderate depression, when delivered entirely via smartphone (rather than involving other human/computerised aspects), and when those using a smartphone mental health intervention are not on any other active treatment for depressive symptoms.(190)

- *Association between diet and mental health disorders in adults* – Epidemiological evidence, cross-sectional studies and prospective studies demonstrate an inverse relationship between diet quality and depression and anxiety in adults. That is, adults having a better quality diet are less likely to be depressed and those with a higher intake of processed and unhealthy foods are at greater risk of anxiety.(191-195)

- *Association between diet and mental health disorders in adolescents and children* - Cross-sectional and prospective studies have shown an association between diet quality and emotional and behavioural problems and depression in adolescents,(196-198) with adolescents on better diets less likely to experience emotional and behavioural problems and depression. And a recent systematic review of 12 epidemiological studies on diet quality and mental health of children and adolescents found evidence of a significant, cross-sectional relationship between unhealthy dietary patterns and poorer mental health in children and adolescents. The authors of this review observed a consistent trend between good quality diet and better mental health and some evidence for the reverse.(199)

- *Dietary advice for people with schizophrenia* - Dietary advice has been shown to improve the dietary intake of the general population but there is little to no research on the impact of dietary advice on those with schizophrenia.(200)

- *Dietary interventions can improve symptoms of depressive disorders but not of anxiety disorders* – A systematic review and meta-analysis was published in 2019 which examining the effect of dietary interventions on symptoms of depression and anxiety. Of the 16 RCTs included in the systematic review/meta-analysis (and n=45,826 participants), all measured depressive symptoms whereas only 11 assessed anxiety outcomes (n=2270 participants). Of the 16 RCTs in the systematic review/meta-analysis assessing symptoms of depression, only one RCT had a sample with clinical depression and the remaining recruiting samples with non-clinical depression. The main analysis found that dietary interventions had a small positive effect on depressive symptoms (g = 0.275, 95% CI = 0.10 to 0.45, p = .002), which remained significant even after adjusting for study quality and publication bias, and the result was seen

[21] Clinical populations included people with major depression, bipolar disorder, and young people in primary care with any mental health condition.
[22] Non-clinical populations refer to people recruited from the general population with self-reported mild to moderate depression, suicidal thoughts/tendencies, probable attention-deficit/hyperactivity disorder, anxiety disorders, insomnia, or symptoms of post-traumatic stress disorder.

in samples with active and non-active controls. No effect of dietary interventions was observed for anxiety. Interestingly, studies with female samples observed significantly greater benefits from dietary interventions, for symptoms of both depression and anxiety.(201)

Traditional therapies for mental health

Depression

- *Acupuncture for depression as an adjunctive therapy* – There is emerging evidence that acupuncture used as an adjunctive treatment with standard medicinal treatments for depression is highly beneficial in reducing the severity of depression by end of treatment, but studies showing this are of low quality.(202)

Schizophrenia

- *Acupuncture for schizophrenia as a monotherapy* – There is limited evidence suggesting that acupuncture may have some antipsychotic effects as measured on global and mental state with few adverse effects for people with schizophrenia.(203)

- *Acupuncture for schizophrenia as an adjunctive therapy* - Acupuncture combined with standard antipsychotic treatment appears to be superior to standard antipsychotic treatment alone, but again, the evidence for this is very low quality.(203)

Evidence of effectiveness of integrative medicine for neurocognitive disorders

Ingestible therapies for neurocognitive disorders

Dementia and mild cognitive impairment (MCI) – Treatment with pharmaceutical grade nutrients and herbal medicines as monotherapies

- *High-dose vitamin B for MCI* – A number of RCTs trials with low risk of bias have shown high-dose vitamin B therapy over a two-year period[23] reduces whole brain and regional grey matter atrophy in cognitively impaired elderly people, with brain atrophy associated with worsening measures of cognitive function.(204-206) The treatment response was found to be related to baseline homocysteine levels: people with higher baseline levels of homocysteine were found to be more responsive to the vitamin therapy (in one study the rate

[23] In these studies, the treatment regime was 0.8mg/day folic acid, 20 mg/day vitamin B6, and 0.5 mg/day vitamin B12.

of atrophy in participants with homocysteine > 13µmol/L was 53 per cent lower in the active treatment group (P=-0.001))(205). Furthermore, individuals with MCI with high baseline blood plasma omega-3 fatty acid levels (>590 µmol/L) compared to individuals with MCI with low baseline blood plasma omega-3 fatty acid levels (<390 µmol/L) have been found to be more responsive to vitamin B therapy to slow brain atrophy.(206)

- *Omega-3 fatty acids for cognitive improvement in patients with MCI and AD*[24] – While there is good evidence that increased dietary intake of fish is associated with reduced risk of cognitive decline or dementia,(207) there is mixed evidence that supplementation of omega-3 fatty acids – such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) found in high abundance in oily fish - has the potential to bring about cognitive improvement in patients with MCI and AD.(208-210)

- *DHA for AD with MCI* - There is some evidence however, that DHA specifically either in supplement form or through consumption of fish in the diet, plays a preventive role in cognitive decline, specifically in people with AD with mild cognitive impairment.(211)

- *Omega-3 fatty acids with antioxidants and other nutrients for mild to moderate AD* – There is evidence that the use of antioxidants and other nutrients in combination with DHA supplementation slows cognitive decline in people with established AD. For example, a proprietorial supplement combination developed for the formation of neuronal membranes, Souvenaid® FortasynH Connect,[25] has clinical utility as an adjunct therapy for people with Alzheimer's disease. Interventions have shown cognitive benefits in people with mild AD rather than mild to moderate AD as a result of FortasynH Connect supplementation. A recent 24-month RCT with just over 300 participants with prodromal Alzheimer's disease found supplementation with FortsynH Connect had no significant effect on the neuropsychological test battery primary endpoint over the two years of the trial, but that cognitive decline in the intervention group was much lower than expected when comparing the intervention group with the control group.(212-215)

- *Omega-3 fatty acids with Alpha-Lipoic Acid (α-LA)*[26] *for AD* – Early research suggests *α-LA* supplementation can play a part in the treatment of AD but larger more robust studies are needed to confirm this preliminary finding.(216) More recent research found combining omega-3 fatty acids with *α-LA* slowed cognitive and functional decline in AD over a 12-month period.(217)

- *Gingko biloba* – the evidence that Gingko biloba provides a predictable and clinically significant benefit for people with dementia or mild cognitive impairment is inconsistent and most trials to date have a high risk of bias.(218-220)

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[24] Omega-3 fatty acids are found in high amounts in oily fish and seafoods and to a lesser extent in grass fed meat, pastured eggs and from a variety of plant-based food stuffs such as walnuts and fresh green vegetables and some nut oils.
[25] Souvenaid® (Nutricia N.V., Zoetermeer, The Netherlands), containing the specific nutrient combination FortasynH Connect, has been designed to enhance synapse formation and function in Alzheimer's Disease. Souvenaid is a product intended as a medical food for oral consumption under medical supervision with the purpose of addressing disease-specific nutrient requirements. The specific nutrient combination Fortasyn Connect comprises docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), uridine-mono-phosphate (UMP), choline, phospholipids, folic acid, vitamins B6, B12, C, E, and selenium, which are the precursors and cofactors for the formation of neuronal membranes.
[26] Alpha-lipoic acid (LA) is a naturally occurring compound found in very low amounts in all foods that is synthesized in the mitochondria. Dietary sources of LA include meat, heart, kidneys, liver, and small amounts from fruits and vegetables.

- *Lemon Balm (Melissa officinalis) for agitation in people with severe dementia* – A trial which randomised 72 residents of a care facility in the United Kingdom to either aromatherapy Lemon Balm or aromatherapy placebo found that aromatherapy with Melissa officinalis was a safe and effect treatment for clinically significant agitation in people with severe dementia: 60 per cent of the active treatment group and 14 per cent of the placebo-treated group experienced a 30 per cent reduction of Cohen-Mansfield Agitation Inventory (CMAI) score, with an overall improvement in agitation (mean reduction in CMAI score) of 35 per cent in patients receiving Melissa balm essential oil and 11 per cent in those treated with placebo.(221)

- *Bacopa monnieri (Brahmi) for cognition and memory in older adults* - A meta-analysis on nine RCTs in older adults found improved executive function and increased attention processing speed in the intervention group supplemented on a daily basis with Brahmi;(222) only two of the nine studies included in the meta-analysis recruited older adults with a complaint of memory impairment. Another meta-analysis on six trials found that Brahmi improved free recall memory in older adults without dementia or significant cognitive impairment.(223)

- *Sage for mild to moderate AD* – Small trials have shown that extracts of sage (*S. officinallis* and *S. lavandulaefolia*) improve attention and memory in individuals with mild to moderate AD.(77, 83) Larger studies with improved methodology and a well-defined herb extract are needed to confirm this finding.

- *Curcumin to prevent cognitive decline* – Epidemiological evidence shows as association between regular consumption of curry and better cognitive performance in healthy older people,(224) and experimental evidence suggesting that curcumin may be neuroprotective of cognitive decline and an effective treatment for dementia.(225-228) A recent randomised, placebo-controlled, double-blind study investigated the ability of a curcumin formulation[27] to prevent cognitive decline in a population of community-dwelling older adults who were healthy. This study found the placebo group experienced a decrease in Montreal Cognitive Assessment score (used to assess general cognitive function) over the 12-month period of the intervention that was not experience in the intervention group.(229)

- *Resveratrol for people with MCI or mild to moderate AD* – To date, only a small number of intervention trials of resveratrol supplementation have been completed in individuals with MCI or mild to moderate AD. While some trials show promising results, at this stage there is insufficient evidence to recommend resveratrol supplementation in individuals with MCI or mild to moderate AD as neuroprotective or with therapeutic effects.(230-232)

- *Anthocyanin[28] for mild to moderate dementia* – A small number of trials have been completed assessing the efficacy of juices high in anthocyanin in improving cognition. An RCT of older adults with mild to moderate dementia (n=49) found daily consumption of a cherry juice high in anthocyanin for 12-weeks resulted in improvements in verbal fluency, short-term memory and long-term memory.(233) However, the results of smaller pilot trials assessing the effect

[27] The intervention group took curcumin BiocurcumaxTM (1500mg per day) for 12-months.
[28] Anthocyanins are a type of flavonoid, a class of compounds with antioxidant effects, which are found naturally in a number of foods. Anthocyanins are the pigments that give red, purple, and blue plants their rich colouring.

of anthocyanin rich juices on cognition in predominantly healthy younger and older people – one using cherry juice(234) and the other using garnet plum juice(235) – concluded there was no effect on cognition. Note that in both pilots, participants only received a 300ml serve of juice (either drunk as one dose of 300mls or in three doses of 100mls (over a two-hour period) on one day.

- *Bioactive constituents of tea may boost cognition in health people but no research has been done to date in people with MCI or dementia* – Data from epidemiological studies suggest that drinking tea (mostly green) may boost cognition, helping to protect the brain against ageing. Green tea consumption is associated with a reduced risk of neurodegenerative diseases such as AD and Parkinson's disease (PD), and higher consumption of green tea is associated with a lower prevalence of cognitive impairment.(236-238) However, no research has been done on the effects of the bioactive constituents of tea on people with MCI or dementia.

- *Ketogenic therapies* – Exogenous ketogenic agents (e.g., medium-chain triglycerides (MCTs), found in high concentrations in coconut oil and palm kernel oil) and dietary manipulation (i.e., carbohydrate restriction and fasting) for neurocognitive disorders are an emerging area of investigation, though clinical evidence is still in its infancy. Ketones may circumvent cerebral metabolic deficits observed in AD (and other neurodegenerative disease) that lead to neuronal death and cognitive impairment.(239-241) One trial reported that dosage compliant (minimum 80 per cent consumption of intended dose) participants with mild AD treated with AC-1202 (patented MCT formulation) for 90-days, differed by -5.33 points in the Alzheimer's disease Assessment Scale-Cognitive Subscale (ADAS-Cog) compared to placebo;(242) a four-point reduction within 6-months is considered clinically meaningful. A similar change (-5 points) in the ADAS-Cog was observed using 56g of MCT daily for 24-weeks, although this was in just one participant.(243) Brain ketone metabolism increased by 230% (measured by FDG-PET) after 6-months of 30g MCT supplementation in participants with MCI. This was associated with secondary changes in cognition, including a 20 per cent improvement in word learning and recall.(244) Increases in regional cerebral blood flow have also been observed after 45-days of 40 g Caprilydene (MCT formula) daily in APOE-ε4 negative participants with AD.(245) Tolerability of MCT appears to be an issue, with gastrointestinal side effects often reported.

- *Modified ketogenic diets* – Are less restrictive than the classic ketogenic diet and have also been used successfully to improve cognition. A very low carbohydrate diet resulted in improved performance in verbal paired association learning,(246) and improvements in episodic memory were observed in adherent participants on a 12-week Modified Atkins Diet.(247) Ketogenic dietary interventions tend to have low compliance and high attrition rates in patients with cognitive impairment. Across most trials, participants lacking the APOE-ε4 allele (strongest genetic risk factor for sporadic AD) saw significantly greater improvements using ketogenic therapies than their APOE-ε4 positive counterparts, who were often no different to placebo at endpoint.

- *Cannabis sativa* – Data from *in vitro* and *in vivo* studies suggests that various cannabinoids derived from *Cannabis sativa* have therapeutic properties relevant to the pathophysiology of AD and MCI. Cannabidiol (CBD) is a non-intoxicating phytocannabinoid derived from

Cannabis sativa and is a promising therapeutic candidate for MCI and AD.(248, 249) CBD has been shown to prevent cortical and hippocampal neurodegeneration, reduce amyloid-beta (Aβ) Aβ production and tau hyperphosphorylation, protect against Aβ neurotoxicity and microglial-activated neurotoxicity, demonstrate anti-inflammatory and antioxidant properties, prevent transcription of pro-inflammatory genes, regulate microglia, promote neurogenesis, and increase cell survival by reducing apoptosis.(250) *In vivo* work has demonstrated both preventative and remedial effects of chronic CBD on cognition in the mouse model for AD.(251, 252) Other cannabinoids including Δ9-tetrahydrocannabinol (THC), linalool, limonene, alpha-pinene, and THCA also have the therapeutic potential to address the diverse symptomology and pathophysiology of AD including anxiety, psychosis, insomnia, restlessness, anorexia, aggression, depression, pain, memory deficits, Aβ plaque formation.(253, 254)

Attention deficit hyperactivity disorder (ADHD) – Treatment with pharmaceutical grade nutrients as monotherapies

- *Omega-3 and omega-6 fatty acids* – There is mixed evidence of the efficacy of omega-3 fatty acids (DHA and EPA) and combinations of omega-3 and omega-6 fatty acids for the treatment of children and adults with ADHD.(255) However, the provision of omega-3 supplements with formulations high in EPA to children with ADHD appears to create modest improvements in symptoms.(256, 257)

- *Zinc* – There is evidence from a large RCT of 400 children and adolescents that high-dose zinc supplementation (150 mg/day) improves ADHD symptoms of hyperactivity and impulsivity (but not inattention). A high drop-out rate of approximately one-in-four participants in each arm, primarily due to protocol violations rather than adverse reactions to the zinc supplement, limits the strength of the finding.(255, 258)

- *Iron* – There is evidence from a small RCT of 23 children (with only five receiving a placebo control) that non-anaemic ADHD children with abnormally low serum ferritin levels benefit from oral iron supplementation (ferrous sulphate 80 mg/day) with improvements in ADHD symptoms compared to placebo.(255, 259)

- *Acetyl-l-carnitine*[29] – The evidence is mixed on the effectiveness of acetyl-l-carnitine as a monotherapy for the treatment of ADHD.(255)

[29] Acetyl-L-carnitine (ALC) is a form of carnitine that's available as a supplement. Carnitine, made by our liver and kidneys, is in most cells of the body and helps cells produce energy.

Attention deficit hyperactivity disorder (ADHD) – Adjunctive treatment of mainstream medical treatments with pharmaceutical grade nutrients

- *Omega-3 fatty acids* – There is no evidence that adjunctive use of omega-3 fatty acids (DHA and EPA) with psychostimulants improves outcomes in children and adults with ADHD beyond that seen with psychostimulant medication alone.(255)

- *Zinc* – There is mixed evidence that zinc used adjunctively to psychostimulants improves outcomes beyond use of a psychostimulant alone.(255)

- *Acetyl-l-carnitine*[30] – Only one RCT has examined if adjunctive use of acetyl-l-carnitine with methylphenidate[31] improves outcomes in children and adolescents with ADHD. Participants (n=40) received either capsules of acetyl-l-carnitine (500 - 1500 mg/day depending on weight) and methylphenidate (20-30 mg/day depending on weight) or placebo plus methylphenidate (20-30 mg/day depending on weight). This study concluded there was no difference between the two groups on the Parent and Teacher Rating Scale scores of ADHD but the group receiving acetyl-l-carnitine reported fewer side effects.(260)

Mind-body therapies for neurocognitive disorders

- *Tai chi for cognitive function in older adults* - Tai chi shows promise as an alternative multi-modal exercise for attenuating age-related cognitive decline – both in healthy older adults and in individuals with MCI through to dementia. A meta-analysis published in 2014 found small to moderate but clinically relevant improvements in executive function in cognitively healthy adults after 10-weeks to one year of tai chi training. The effect size was larger when tai chi was compared with non-intervention controls (Hedges' g = 0.90; P = .04) than when tai chi was compared with an active control[32] (Hedges' g = 0.51; P = .003). When data relating to cognitively impaired adults was examined smaller but statistically significant effects were found when tai chi was compared with a non-intervention control (Hedges' g = 0.346, P = .004, I2 = 0%).(261) This finding is supported by the findings of a systematic review published in 2015 which found healthy adults practising tai chi on a regular basis showed better performance on several cognitive tasks compared to those doing usual physical activity.(262)

- *Yoga for cognitive function in older adults* - While a meta-analysis of randomised controlled trials involving asana-based yoga found that this practice can ameliorate risk factors for metabolic syndrome (aside from insulin resistance),(263) the effectiveness of yoga in modifying cognitive decline risk and improving cognitive decline is yet to be investigated using clinical trials.

[30] Acetyl-L-carnitine (ALC) is a form of carnitine that's available as a supplement. Carnitine, made by our liver and kidneys, is in most cells of the body and helps cells produce energy.
[31] Methylphenidate, which is sold under the trade name Ritalin among others, is a stimulant medication used to treat ADHD.
[32] The active controls in this instance were Western exercise, cognitive behaviour therapy or mahjong.

Manual therapies for neurocognitive disorders

- *Massage and touch for dementia* – A recently published systematic review and meta-analysis of massage and touch on behavioural and psychological symptoms of people with dementia found massage and touch were effective in reducing behavioural and psychological symptoms associated with dementia, specifically physical aggressive behaviour, physical non-aggressive behaviour, verbal aggressive behaviour, and non-verbal aggressive behaviour. This study found the impact on anxiety, sadness and anger were not significant. While the review findings were positive, the studies included in this systematic review and meta-analysis were small and of poor methodological quality.(264)

Lifestyle Therapies for neurocognitive disorders

- Epidemiological evidence suggests physical activity has an independent preventive effect on cognitive decline and the development of AD(265-267) and may decrease the risk of PD.(268-270)

- *Exercise and MCI* - A World Health Organization report published in 2019 on lifestyle modifying strategies to reduce cognitive decline and dementia risk concluded that older adults should perform aerobic exercise at moderate to vigorous intensities, together with muscle-strengthening activities, for at least 150-minutes throughout the week to maintain or improve cognition.(271) This conclusion was based on systematic reviews of physical activity interventions involving aerobic, resistance or multicomponent training in adults with normal cognition or mild cognitive impairment (MCI) which found that exercise at the highest level was most protective for brain health,(272, 273) with individuals with MCI showing exercise-induced enhancements in certain cognitive domains.(274, 275)

- *Exercise to attenuate neurodegeneration* - Aside from the evidence listed above, there is good evidence from neuroimaging studies that exercise attenuates age-related neurodegeneration in clinical and non-clinical adult populations, with exercise preventing decreases in hippocampal volume which occur over time as people age.(188) Furthermore, people who actively participate in physical activity in midlife tend to have larger total brain volume in later-life than sedentary people (with this difference more apparent in grey matter volume than white matter volume).(276)

- *Exercise for people with dementia* – A Cochrane review published in 2015 assessed if exercise programs for people with dementia improves cognition[33], activities of daily living, neuropsychiatric symptoms such as agitation and aggression, depression and mortality, among other outcomes. This review found there was some evidence that exercise programs can improve the ability of people with dementia to perform daily activities, but found no

[33] Cognition includes such things as memory, reasoning ability and spatial awareness.

evidence of benefit of exercise on cognition, psychological symptoms, and depression in people with dementia.(277)

- *Exercise and the impact on disease progression of AD and PD* – There is no consistent evidence that physical activity positively impacts the disease progression of AD(278, 279) and PD.(280, 281)

- *Multi-domain lifestyle interventions protective of cognitive health* – A seminal RCT was completed over two-years in Finland in the early 21st-century – The FINISH Trial[34] – and found that a lifestyle intervention having a number of domains focused on different risk factors for dementia is likely effective in preventing cognitive decline. The two-year multi-domain intervention focused on physical activity, nutritional guidance, cognitive training, social activities, and management of heart health risk factors. The study authors concluded participants randomised to the intervention arm showed improved cognition when compared to those provided with general health advice. The multi-domain intervention was protective of cognitive function in healthy older adults at increased risk of cognitive decline.(282) The multi-domain lifestyle model used in the FINGER trial is now being tested in different populations and settings across the world, with RCTs starting recruitment in 2018 in the United States of America (US-Pointer) and China (MIND-CHINA), and other countries more recently.(283)

- *Mediterranean diet for cognitive health* - Systematic reviews of observational studies have found that a high adherence to the Mediterranean diet is associated with decreased risk of MCI and AD, whereas just a modest adherence to this diet does not show this same association.(284, 285) Among participants with normal cognition, the strongest evidence suggests a beneficial effect of the Mediterranean diet on older adults global cognition.(286)

Traditional therapies for neurocognitive disorders

- *Acupuncture* –There is no evidence that from human clinical trial data acupuncture is an appropriate treatment modality to improve cognition for people with neurocognitive disorders.

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Acknowledgements

NICM Health Research Institute would like to acknowledge Professor Jerome Sarris, Associate Professor Genevieve Steiner and Dr Joe Firth, Western Sydney University, Professor Andrew Scholey, Swinburne University and Dr Wolf Marx, Deakin University, for their contribution and expert input.

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Suggested citation for this therapeutic outline:
NICM Health Research Institute. Integrative medicine for mental health and neurocognition – a therapeutic outline. Westmead: NICM Health Research Institute, Western Sydney University; 2021.

Date last updated: March 2021