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Geriatric Disorders (M Sajatovic and A Aftab, Section Editors)

Emerging Complementary and Integrative Therapies for Geriatric Mental Health

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Abstract

Purpose The use of complementary and integrative medicine (CIM) is on the rise among diverse populations of older adults in the USA. CIM is commonly perceived as safer, less expensive, and more culturally acceptable. There is a growing body of evidence to support the use of CIM, especially mind-body therapies, diet and nutritional supplements used for mental disorders of aging.
Recent findings We summarize the results of the recent clinical trials and meta-analyses that provide the evidence for the role of CIM in treating older adults with mood or cognitive disorders that includes the use of diet and supplements, and mind-body therapies.
Summary Dietary and mind-body therapies have become increasingly popular and show the strongest evidence of efficacy for mood and cognitive disorders. Although the use of vitamins and supplements is the most popular CIM practice, only mixed evidence supports their use with additional concerns for herb (supplement)-drug interactions. Despite increasing use of CIM by the general population, information to guide clinicians providing care for older adults remains limited with variable scientific rigor of the available RCTs for a large number of commonly used CIM interventions for the mental health of older adults.

Introduction

Acceptance and use of complementary and integrative medicine (CIM) therapies is growing, especially among the Baby Boomers cohort born in 1946–1964, and later birth cohorts [1]. CIM has been widely used in many different cultures dating back to the eighteenth century, starting with homeopathy and ancient healing traditions, such as Traditional Oriental Medicine (TOM) (e.g., Traditional Chinese Medicine (TCM), acupuncture, shiatsu, and reiki), Indian systems of healthcare (e.g., Ayurveda and yoga), and Native American healing practices (e.g., Sweat Lodge and Talking Circles). All integrative practices share the belief that wellbeing is a state of balance in the spheres encompassing the spiritual, physical, and mental/emotional functioning that can be achieved by leading a balanced healthy lifestyle ensured by proper nutrition, exercise, sleep habits, and the ability to regulate stress response via meditation or other mind-body practices. Because CIM is often considered to be a natural and safer option compared to conventional medicine in addressing common health conditions, these interventions are rapidly gaining popularity in the USA [1, 2]. Many of these practices fall into the category of lifestyle medicine where individuals are empowered to make healthier choices in diet, exercise, sleep, and stress management. Lifestyle medicine is a new emerging field of integrative medicine that offers relatively simple and often low-cost solutions to treatment and prevention of aging-related mental and physical disorders. Lifestyle interventions include, but are not limited to nutrition and the use of supplements, aerobic and mindful physical exercise, stress reduction, intermittent fasting, and smoking cessation [3]. In cases of mind-body practices, individuals go through training to develop life-long skills for self-regulation in face of adversity and stress, and health promoting practices that improve immune functioning that is especially important during the COVID-19 pandemic (e.g., by practicing basic hygiene, improving sleep quality, diet that includes rainbow-colored fruit and vegetables, proper exercise routine, stress reduction including meditation and yoga). The COVID-19 pandemic highlighted the general importance of health-promoting practices.

Although the terms, "alternative," "complementary," and "integrative" are often used interchangeably, the National Center for Complementary and Integrative Health (NCCIH) defines these terms as follows: "alternative" medicine refers to a set of practices of medicine (e.g., traditional, oriental, mind-body, etc.) without sufficient evidence base that is used in place of conventional medicine, whereas "complementary" medicine refers to non-mainstream practice that is used together with conventional medicine. "Integrative" medicine refers to the use of conventional and complementary approaches in a coordinated way targeting specific disorders or underlying neurobiological processes (e.g., inflammation). CIM emphasizes a holistic, patient-focused approach to healthcare and wellness targeting the whole person rather than one organ system. Historically, these practices are oriented toward harmonious rebalancing of mind, body, and spirit. The NCCIH identified three categories for complementary and integrative approaches: (1) natural products (herbal medicines, botanicals, vitamins, minerals, probiotics, and other dietary supplements); (2) mind and body practices (massage therapy, meditation, yoga, acupuncture, chiropractic/osteopathic manipulation, hypnotherapy, tai chi, qigong, healing touch, and relaxation exercises); (3) other complementary approaches (indigenous healing practices, Chinese medicine, Ayurvedic medicine, homeopathy, and naturopathy).

Unfortunately, CIM is rarely included in the healthcare systems on the large scale with the exception of a few modalities (i.e., acupuncture and chiropractic care) due to the lack of reimbursement by the US medical insurances, and remain unaffordable for many older adults living on a limited income [4]. Billions of dollars are spent out of pocket per year on a poorly regulated large health-promotion industry with unvalidated health outcome claims and with limited evidence and can be confusing to navigate for the consumers, and especially for older adults. In this review, we focus on the most popular CIM modalities with the strongest evidence, including diet and mind-body therapies used for commonly occurring mood, anxiety, and cognitive disorders.

Complementary and integrative medicine use in the USA

In a joint survey conducted by the American Association of Retired People (AARP) and the NCCIH, the use of CIM was reported to be have increased rapidly, exceeding a prevalence of 53% among those aged 50 years and above [5]. Previously, studies had shown that older adults were more likely to use prayer for health and spiritual practices than younger adults, and were less likely to use other forms of CIM [6]. However, a recent study comparing the Baby Boomers cohort (1946–1964) to the pre-boomer cohort (those born prior to 1946) demonstrated that a higher proportion of Baby Boomers used CIM (27.7%) than pre-boomers (16.4%). [6]

Aging is associated with chronic mental, cognitive, and physical conditions. The use of CIM offers less invasive, more cost-effective, culturally acceptable, and scalable therapies [7]. There has been a robust increase in use of yoga, tai chi, and qigong from 2002 to 2017 (5.8 to 14.5%, respectively) by the general population typically for stress, anxiety, and depression [8]. Therefore, clinicians treating older adults need to be informed of the efficacy and potential side effects of various CIM therapies to better assist their patients in making healthcare decisions.

Diet and use of nutritional and herbal supplements

Several lines of investigation have pursued the role of diet and nutrition in management of mental disorders. These include targeting increased oxidative stress and inflammation, reduced essential nutrients in psychotic and mood disorders, and gut microbiome dysfunction, all of which have been linked to mental disorders. Over a half of all US adults take some form of nutritional supplements. Older adults age 70 and older suffering from disorders, such as stroke, cancer, obesity, breathing problems, and arthritis are more likely to use herbal and nutritional supplements [9]. Despite the popular belief that natural supplements are safer, their use can be associated with important adverse effects and supplement/herb-drug interactions, which is only minimally regulated by the Food and Drug Administration (FDA). Additionally, excessive consumption of certain supplements may be harmful, under-reported in the consumer reports or media, and under-appreciated by patients and healthcare providers [10].

The emerging field of nutritional psychiatry focuses on the consequences and associations between what you eat, how you feel, and ultimately, how you behave. The focus shifts from single nutrients or supplements to a comprehensive, cohesive, and scientifically rigorous evidence base to support a shift in thinking about the role of diet and nutrition in mental health [11]. The studies of the impact of diet on symptoms of depression, anxiety, and cognitive decline are summarized in Table 1. In particular, the Mediterranean diet gained attention after a large, multicenter, randomized controlled "the PREDIMED" study [12, 13] showed that adherence to a Mediterranean diet can be a primary prevention strategy for cardiovascular disease. The Mediterranean diet consists

Table 1. Study characteristics of diet and supplements

Reference	Study design	Intervention	Study sample	Findings/effect
Depression				
Jacka et al. 2017	RCT	MedDiet for depression	65 patients, ages 18 and older	*Significant effect* of MedDiet on improvement on MADRS between baseline and 12 weeks
Parletta et al. 2019	RCT	MedDiet + fish oil on depression	95 patients, age 18–65, moderate-severe depression	*Significant effect* of MedDiet, supplemented with fish oil, on improving depression and QoL scores
Vicinanza et al. 2020	Cross-sectional study	MedDiet on depression	143 patients, age 65 and over	Significant association between MedDiet and depression.
Cherian et al. 2020	Observational prospective cohort study	Mediterranean-DASH diet on depression	709 patients, age 65 and over	DASH diet scores had lower rates of depressive symptoms compared to positive association of Western diet with depression.
Young et al. 2019	Meta-analysis	B vitamin supplementation on depressive symptoms, anxiety, stress	958 participants, ages 18 and over	Some positive effect of B vitamins over a placebo for stress ($n = 958$, SMD = 0.23, 95% CI = 0.02, 0.45, $p = 0.03$) but not on depression ($n = 568$, SMD = 0.15, 95% CI = – 0.01, 0.32, $p = 0.07$), or anxiety ($n = 562$, SMD = 0.03, 95% CI = – 0.13, 0.20, $p = 0.71$).
de Koning et al. 2019	RCT	Vitamin D supplementation for depressive symptoms and physical functioning	155 participants, ages 60–80 years old	Supplementation of vitamin D for 12 months had *no effect* on depressive symptoms, physical functioning in older adults with low levels.
Galizia et al. 2016	Cochrane review	SAMe supplement for depression	934 participants, adults	*No strong evidence* of a difference in terms of change in depressive symptoms from baseline to end of treatment between SAMe and placebo as monotherapy (SMD – 0.54, 95% confidence interval (CI) – 1.54 to 0.46; $p = 0.29$;

Table 1. (Continued)

Reference	Study design	Intervention	Study sample	Findings/effect
				142 participants; 2 studies; very low quality evidence); low quality evidence that SAMe is superior to placebo as add-on to SSRIs in terms of change in depressive symptoms from baseline to end of treatment (MD – 3.90, 95% CI – 6.93 to – 0.87; $p = 0.01$; 73 participants; 1 study.
Sharma et al. 2017	Systematic review	SAMe supplement for depression	878 participants in 19	placebo-controlled RCT and 1591 participants in 21 RCTs vs antidepressants in adults
Limited evidence of efficacy and safety of SAMe as a monotherapy and augmentation for other antidepressants				
Linde et al. 2008	Cochrane review	SJW for depression	5489 participants, 29 trials, adults	*Significant but possibly variable effect* of SJW to placebo for mild-moderate MDD, similarly effective as antidepressants and had fewer side effects than antidepressants. In nine larger trials the combined response rate ratio (RR) for hypericum extracts compared with placebo was 1.28 (95% confidence interval (CI), 1.10 to 1.49) and from nine smaller trials was 1.87 (95% CI, 1.22 to 2.87). Results of trials comparing hypericum extracts and standard antidepressants were statistically homogeneous. Compared with tri- or tetracyclic antidepressants and

Table 1. (Continued)

Reference	Study design	Intervention	Study sample	Findings/effect
				selective serotonin reuptake inhibitors (SSRIs), respectively, RRs were 1.02 (95% CI, 0.90 to 1.15; 5 trials) and 1.00 (95% CI, 0.90 to 1.11; 12 trials).
Ng et al. 2017	Meta-analysis	SJW for depression	3808 participants, 27 RCTs, adults	SJW has *comparable efficacy* and safety compared to SSRIs for mild-moderate depression. In patients with depression, St. John's wort demonstrated comparable response (pooled RR 0.983, 95% CI 0.924–1.042, $p < 0.001$) and remission (pooled RR 1.013, 95% CI 0.892–1.134, $p < 0.001$) rate, and significantly lower discontinuation/dropout (pooled OR 0.587, 95% CI 0.478–0.697, $p < 0.001$) rate compared to standard SSRIs. The pooled SMD from baseline HAM-D scores (pooled SMD – 0.068, 95% CI – 0.127 to 0.021, $p < 0.001$) also support its significant clinical efficacy in ameliorating depressive symptoms.
Anxiety				
Miyasaka et al. 2006	Cochrane review	Valerian root for anxiety	36 participants, ages 16 and older, one pilot study	*No clear safety or efficacy* compared to placebo or diazepam for anxiety. Based on the HAM-A scale overall score at post-treatment, no significant difference in symptom reduction was noted between valerian and placebo (WMD – 1.40, 95%CI -7.93 to 5.13). No significant difference in symptom

Table 1. (Continued)

Reference	Study design	Intervention	Study sample	Findings/effect
				reduction was noted between valerian and diazepam (WMD 0.40, 95% CI – 6.22 to 7.02).
Cognition				
		Martínez-Lapiscina et al. 2013	RCT	MedDiet (supplemented with either extra-virgin olive oil (EVOO) or mixed nuts) versus a low-fat control diet for cognition
522 patients, ages 55 to 80	*Significant effect* of MedDiet enhanced with either EVOO or nuts on improving cognition compared with a low-fat diet.			
Loughrey et al. 2017	Meta-Analysis	MedDiet on cognition	41,492 participants (15 cohort studies) and 309 participants (2 RCTs), age 50 and over	*Significant effect* of the MedDiet and episodic memory ($n = 25,369$, $r = 0.01$, $p = 0.03$) and global cognition ($n = 41,492$, $r = 0.05$, $p \leq 0.001$), but not working ($n = 1487$, $r = 0.007$, $p = 0.93$) or semantic memory ($n = 1487$, $r = 0.08$, $p = 0.28$)
D'Amico et al. 2020	Cross-sectional study	MedDiet on stress and cognition	192 participants, age 60–95 years old	Significant association between higher perceived stress and poorer executive function with lower adherence to MedDiet
Burckhardt et al. 2016	Cochrane review	Omega-3-PUFA supplements on mild to moderate AD over six, 12 and 18 months	632 participants including 3 RCTs	*No strong evidence* for the efficacy of omega-3 PUFA supplements in the treatment of mild to moderate AD. Alzheimer's Disease Assessment Scale - Cognitive subscale (SMD – 0.02, 95% confidence interval (CI) – 0.19 to

Table 1. (Continued)

Reference	Study design	Intervention	Study sample	Findings/effect
				0.15; 566 participants; 3 studies; high quality evidence) or Mini-Mental State Examination (MD 0.18, 95% CI – 1.05 to 1.41; 202 participants; 2 studies; high quality evidence) or on activities of daily living (SMD – 0.02, 95% CI – 0.19 to 0.16; 544 participants; 2 studies; high quality evidence); no difference at 6 months of treatment on severity of dementia measured with the Clinical Dementia Rating - Sum of Boxes (MD – 0.00, 95% CI – 0.58 to 0.57; 542 participants; 2 studies; high quality evidence) or on quality of life measured with the Quality of Life Alzheimer's Disease scale (MD – 0.10, 95% CI – 1.28 to 1.08; 322 participants; 1 study; high quality evidence). There was no difference at 6 months on mental health measured with the Montgomery-Åsberg Depression Rating Scale (SMD – 0.10, 95% CI – 0.74 to 0.54; 178 participants: 1 study; high quality of evidence) or the Neuropsychiatric Inventory (SMD 0.10, 95% CI – 0.07 to 0.27; 543 participants; 2 studies; high quality of evidence).
Yang et al. 2015	Meta-analysis	*Ginkgo biloba* for cognition (MCI and AD)	2608 participants in 21 RCTs, adults	Ginkgo biloba in combination with conventional medicine was superior in improving

Table 1. (Continued)

Reference	Study design	Intervention	Study sample	Findings/effect
				Mini-Mental State Examination (MMSE) scores at 24 weeks for patients with Alzheimer's disease (MD 2.39, 95% CI 1.28 to 3.50, $p < 0.0001$) and mild cognitive impairment (MD 1.90, 95% CI 1.41 to 2.39, $p < 0.00001$), and Activity of Daily Living (ADL) scores at 24 weeks for Alzheimer's disease (MD – 3.72, 95% CI – 5.68 to – 1.76, $p = 0.0002$).

MedDiet Mediterranean diet, *EVVO* extra-virgin olive oil, *MADRS* Montgomery–Åsberg Depression Rating Scale, *QoL* quality of life scale, *DASH* Dietary Approaches to Stop Hypertension, *PUFA* polyunsaturated fatty acids, *AD* Alzheimer's disease, *SAMe* S-adenosyl-L-methionine, *MCI* mild cognitive impairment, *SJW* St. John's wort, *MDD* major depressive disorder

of plentiful use of olive oil; high consumption of fruit, vegetables, legumes, cereals, and nuts; regular, but moderate intake of wine (especially red wine) with meals; moderate consumption of fish, seafood, fermented dairy products (yogurt and cheese), poultry, and eggs; and limited consumption of red and processed meats and sweets. Additionally, there are emerging observational studies examining the impact of green tea on cognition and aging with promising results [14].

Mood and anxiety disorders

Two RCTs, one by Jacka et al. [15] and Parletta et al. [16], found significant improvement in depression with Mediterranean diet interventions in adults compared to social support controls. Jacka and colleagues [15] found that the dietary support group demonstrated significantly greater improvement between baseline and 12 week MADRS scores compared to social support alone, while Parletta and colleagues [16] found a greater reduction in depression ($p = 0.03$) and improved mental health quality of life (QoL) scores ($p = 0.04$) at 3 months with sustained effects at 6-month follow-up with Mediterranean and fish oil supplementation compared to social support alone. Similarly, a cross-sectional, observational study in older adults suggested that adherence to a Mediterranean diet lead to less depressive symptoms [17]. A more recent, large RCT by Ghosh et al. [18] showed a strong relationship between a Mediterranean diet and promotion of overall healthier aging through changes in gut microbiota. Another observational cohort study by Cherian et al. [19] examined the relationship between Mediterranean-Dietary Approaches to Stop Hypertension (DASH) diet on depression in older adults,

demonstrating adherence to the Mediterranean-DASH diet associated with lower rates of depression while Western diets had a positive association with depression.

Cognition

Beyond mood effects, the Mediterranean diet has also shown to be beneficial for cognition. One of the first randomized control trials examining dietary pattern on global cognitive function by Martínez-Lapiscina and colleagues [12] demonstrated nutritional intervention with the Mediterranean diet supplemented with either extra virgin olive oil (EVOO) or mixed nuts is associated with improved global cognition, independent of potential confounders such as age, family history of cognitive impairment or dementia, apolipoprotein E (ApoE) genotype, education, physical activity, vascular risk factors, and energy intake. Similarly, a prospective study by Morris and colleagues [20] examined three dietary patterns (Mediterranean diet, the DASH diet, and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet) and showed that high adherence to all three diets may reduce Alzheimer's disease (AD) risk, with moderate adherence to the MIND diet also decreasing AD risk. Similar to the Mediterranean diet, the DASH diet specifies a high consumption of plant-based foods but also limits the intake of saturated and total fat, cholesterol, and sodium; it was initially developed to target hypertension and cardiovascular risk factors. The MIND diet emphasizes natural plant-based foods as well as consumption of berries and green leafy vegetables while limiting animal foods and saturated fats [21]. More recently, a large meta-analysis by Loughrey et al. [22•] included 15 cohort studies, with 2 RCTs revealing a significant association between the Mediterranean diet and improvement in episodic memory ($p = 0.03$) and global cognition ($p < 0.001$), but not working memory ($p = 0.93$) or semantic memory ($p = 0.28$). [22•] Another recent observational study by D'Amico and colleagues demonstrated that a higher adherence to a Mediterranean diet is associated with lower perceived stress and executive dysfunction [23].

Unlike supplements where the data has been less consistent, certain dietary patterns have shown stronger, reproducible evidence to support mental health. It is likely that a combination of emphasizing foods that contain multiple beneficial nutrients, as well as reduction in saturated and unsaturated fats, has a stronger, combined effect on mental disorders than single supplementation alone.

Use of nutritional and herbal supplements

Along with regular food consumption, nutrients can also be consumed in herbal and nutritional supplement form that is the most popular form of complementary therapy in older adults. Only a few supplements used for mood and cognitive disorders have robust research evidence of efficacy and safety. There have been several approaches to recent clinical research regarding mental

disorders and diet and nutrition. These include targeting increased oxidative stress and inflammation, reduced essential nutrients in psychotic and mood disorders, and gut microbiome dysfunction, all which have been linked to mental disorders [3]. Many nutritional supplements have been studied for their potential role as neuroprotective interventions in AD and cognitive disorders in older age. Some of the more popular supplements marketed for memory enhancement are fish oils (omega-3 fatty acids), B vitamins (e.g., folate, B6, and B12), and *Ginkgo biloba* extract [24]. The studies of the impact of supplements on symptoms of depression, anxiety, and cognitive decline are summarized in Table 1.

Vitamins

Although antioxidant compounds such as vitamins A, C, and E have a role in regulation of oxidative stress, a pathway linked with neurodegeneration and cognitive decline, the use of vitamin E has not been found to have a significant effect on progression from MCI to dementia and/or AD, or on cognitive function at intervention completion [25]. Similarly, low folate and B vitamin status is linked to cognitive dysfunction during the aging process and better cognitive performances have been associated with higher intakes of B vitamins. Although B vitamin supplementation (folic acid, vitamin B6, and B12 combination) have resulted in reduced rates of brain atrophy in MCI, findings are mixed with meta-analyses of clinical trial data reporting no significant effect of B vitamins on cognitive function [25]. A more recent meta-analysis of B vitamin supplementation for depression and anxiety showed some benefit from stress but no significant effect on depression or anxiety [26]. Lower levels of vitamin D have been observed in populations suffering from depressive disorders. However, in a recent RCT, supplementation with 1200 IU/day vitamin D for 12 months had no effect on depressive symptoms and physical functioning in older persons with relatively low vitamin D status, clinically relevant depressive symptoms, and poor physical functioning [27]. Similarly, another recent review indicated contradictory information between vitamin D for treatment of depressive symptoms [28]. Similarly, although human studies strongly support a correlation between low levels of circulating 25-hydroxyvitamin D (25(OH)D) and cognitive impairment or dementia in aging populations, prior clinical interventional studies have failed to associate increased 25(OH)D levels with improved cognitive outcomes. [29]

Omega-3 fatty acids, which include eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha linolenic acid (ALA), have been extensively studied over the past two decades. However, results are mixed likely due to heterogeneity among studies regarding omega-3 preparations, doses, and study design since there are inconsistencies in administering EPA or a combination of EPA and DHA, mostly as an adjunct therapy for unipolar depression but also as monotherapy [30]. In addition to depression and anxiety, fish oil's PUFAs have also been associated with promoting cognitive function, primarily as a result of their anti-inflammatory properties. Additionally, n-3 fatty acids, particularly DHA, are a key component of neuronal membranes in the brain, influencing neurogenesis and neuronal function [31•]. In a recent Cochrane review by Burckhardt et al. [31•]

looking at the effects of omega-3 fatty acids for the treatment of dementia, three comparable randomized, placebo-controlled trials investigating omega-3 PUFA supplements in 632 participants with mild to moderate AD over 6, 12, and 18 months were examined. However, there was no evidence of a benefit from omega-3 PUFAs on cognitive function when measured at 6 months with the Alzheimer's Disease Assessment Scale-Cognitive subscale or Mini-Mental State Examination or on activities of daily living. [31•]

S-adenosylmethionine (*SAMe*), an endogenous, intracellular amino acid metabolite and enzyme co-substrate involved in multiple crucial biochemical pathways, including biosynthesis of hormones and neurotransmitters, has been implicated in depression and cognition. Additionally, deficiencies of folate and vitamin B12, necessary co-factors in the synthesis of SAMe, may account for decreased SAMe levels, especially in patients with depression and dementia. A recent Cochrane review by Galizia et al. [32] and recent review by Sharma et al. [33•] looked at over 50 clinical trials in the USA and Europe examining SAMe in the treatment of depressive disorders with some encouraging evidence of efficacy and safety of SAMe as a monotherapy when compared to placebo as well as antidepressant augmentation. SAMe also had a much more favorable side effect profile and minimal drug-drug interactions. However, the data remains largely inconclusive given the overall power was low to modest and results need further investigation to establish stronger evidence [32, 33•].

Gingko biloba has been studied in cognitive cohorts with mixed results. In a systemic review and meta-analysis by Yang et al. [34], 21 trials were found examining the effects of *Ginkgo biloba* on cognition. They concluded that when compared with treatment as usual alone, *Ginkgo biloba* in combination with treatment as usual was superior in improving Mini-Mental State Examination (MMSE) scores at 24 weeks for patients with Alzheimer's disease ($p < 0.0001$) and mild cognitive impairment ($p < 0.00001$), and Activity of Daily Living (ADL) scores at 24 weeks for Alzheimer's disease ($p = 0.0002$). However, when compared with placebo or conventional medicine in individual trials, *Ginkgo biloba* demonstrated similar but inconsistent findings. It is important to note that *Ginkgo biloba* can increase risk of bleeding when combined with warfarin due to inhibition of platelet-activating factor (PAF), raise blood pressure when combined with a thiazide diuretic, and increase risk of coma when combined with trazodone [35].

St. John's Wort

There are over 40 published clinical trials of St. John's wort (*Hypericum perforatum* (SJW), including many comparisons with tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) that have been published over the past decade [30]. A Cochrane review by Linde et al. [36] examined 29 trials including 5489 patients; 18 trials compared SJW with placebo, and 17 compared it with standard antidepressants. Results showed heterogeneity, but overall, SJW was found to be superior in efficacy to placebo and equivalent to standard antidepressants, with better tolerability. A meta-analysis Ng et al. [37] of 27 clinical trials with a total of 3808 patients were reviewed, comparing the use of St John's wort and SSRI. In

patients with depression, St John's wort demonstrated comparable response ($p < 0.001$) and remission ($p < 0.001$) rate, and significantly lower discontinuation/dropout ($p < 0.001$) rate compared to standard SSRIs. The evidence thus far supports SJW for treatment of depressive disorders, although it may be less effective in chronic and/or severe depression. However, it is important to note that SJW can induce P-glycoprotein and/or cytochrome P450 (CYP) enzymes (particularly CYP 3A4) by SJW due to numerous reports indicating the possibility of important interactions with prescribed drugs. SJW has been shown to lower the plasma concentration (and/or the pharmacological effect) of a number of drugs including alprazolam, amitriptyline, cyclosporine, digoxin, fexofenadine, indinavir, irinotecan, methadone, nevirapine, simvastatin, tacrolimus, theophylline, warfarin, phenprocoumon, and oral contraceptives, as well as cause serotonin syndrome when combined with serotonin reuptake inhibitor, antidepressants (e.g., sertaline, paroxetine, nefazodone), or buspirone [35].

Valerian root (*Valeriana officinalis*) is the most commonly used herbal supplement for sedation and anxiolysis and has been used worldwide for over 1000 years and may function similarly to benzodiazepines or barbiturates, with GABA-ergic activity [30, 38]. One RCT involving 36 patients with generalized anxiety disorder was a 4-week pilot study of valerian, diazepam and placebo, but no significant differences between the valerian and placebo groups or valerian and diazepam groups were found in HAM-A total scores [39].

A small number of studies examined the use of herbs and supplements in anxiety disorders. However, in a recent study looking to identify herbals showing interaction with the GABA system, in addition to human clinical trials, ten herbals were identified: kava, valerian, pennywort, hops, chamomile, *Ginkgo biloba*, passionflower, ashwagandha, skullcap, and lemon balm. Collectively, the literature reveals preclinical and clinical evidence for various herbals modulating GABA-pathways, with comparative anxiolytic effect to the current array of pharmaceuticals, along with good safety and tolerability profiles [40]. In particular, there is some data to support the effectiveness of kava compared popular supplements like St. John's wort, valerian, and omega-3 fatty acids for anxiety [41]. Although side effects for these supplements are minimal, Kava can increase "off" periods in Parkinson patients taking levodopa and can cause a semi-comatose state when given concomitantly with alprazolam [35].

Mind-body therapies

Mind-body therapies (MBTs) are also rising in popularity according to the 2017 National Health Survey with the 5–10% increased use of yoga, meditation and chiropractic care in the last 5 years [42•]. A growing body of research evidence supports the use of MBTs (including meditation, yoga, tai chi, and qigong) as minimally invasive, cost-effective approaches for the management of stress, late-life mood, and cognitive disorders. In contrast to pharmacological approaches, MBTs aim to teach patients life-long skills that may continue to confer

benefits long after formal training has ended. Continued research in this area will promote the integration of MBTs into mainstream clinical practice and help to alleviate the increased chronic health burden of an aging population. Existing evidence suggests that, on average, both meditative movement (e.g., yoga) and multicomponent mindfulness-based interventions (e.g., mindfulness-based cognitive therapy (MBCT) and mindfulness-based relapse prevention (MBRP)) can be as effective as other active treatments for disorders such as major depression, anxiety, and substance use disorder. Results of studies with healthy adults suggest that multicomponent interventions such as mindfulness-based stress reduction (MBSR) have potential to increase empathy, self-control, self-compassion, relationship quality, and spirituality, as well as decrease rumination. Research has also begun to evaluate the neurobiological mechanisms, by which meditative therapies enhance resilience to mental health disorders, and several promising mechanistic domains (neural, hormonal, immune, cellular, and cardiovascular) have been identified [43]. Mindfulness-based treatment protocols are usually brief (typically eight in-person individual or group sessions), multi-component interventions incorporating both education and practice. Two of the most commonly available and widely studied forms in research are MBSR and MBCT [43]. Yoga therapy is also becoming very popular especially among younger adults [42•]. We have previously published the results of the randomized clinical trials documenting the effects of yoga, tai chi, and meditation in older adults with depression and cognitive decline identifying therapeutic benefits for mood, anxiety, resilience, and cognition, accompanied by physiological anti-inflamatory effects, as well as improved brain neuroplasticity and connectivity [44–52]. The studies of the impact of mind-body therapies on symptoms of depression, anxiety, and cognitive decline are summarized in Table 2.

Mood disorders

The most recent meta-analysis of 11 RCTs with 12 MBT treatment arms found that mindfulness-based interventions (MBIs) showed significant improvement in depressive symptom severity compared to control groups at post-MBI assessment. However, the effect was not significant at the end of the follow-up and endpoint assessment period [43]. Another meta-analysis of 12 RCTs of mindfulness-based interventions for individuals with a current depressive or anxiety disorder found that mindfulness-based interventions significantly decreased primary symptom severity compared to a mixed control group including both active (e.g., cognitive behavior therapy, psychoeducation) and inactive (e.g., treatment as usual) control conditions but this positive effect also appeared limited to post-MBI assessment but not at the end of follow-up period [43]. Another meta-analysis on individual patient data from 9 RCTs examined the efficacy of MBCT compared with usual care and other active treatments (including antidepressants) in treating adults with recurrent depression [53]. Results indicated that patients who received MBCT had a reduced risk of relapse within a 60-week follow-up period compared with those who did not. Individuals with more severe depression pre-treatment experienced greater benefits with of MBCT compared to controls. Another meta-analysis investigated the

Table 2. Study characteristics of MBTs

Reference	Study design	Intervention	Study sample	Findings
Depression				
Wang et al. 2018	Meta-analysis	MBIs, including MBCT, MBSR, on depression	11 RCTs, $N = 764$, adults ages 18 and older	MBIs (MBCT, MBSR) were associated with reduction of depression severity immediately after MBIs but not at follow-up endpoint. Compared to the control group, MDD subjects receiving MBIs showed significant reduction in depressive symptoms ($n = 722$; SMD – 0.59, 95% CI – 1.01 to – 0.17, $I^2 = 85\%$, $p = 0.006$) at post-MBI assessment, but the significance disappeared by the end of post-treatment follow-up.
Strauss et al. 2014	Meta-analysis	MBIs on depression and anxiety	12 RCTs, $N = 578$, adults ages 18 and older	*Significant effect* on post-intervention between-group benefits of MBIs on depression but *not* on anxiety. Significant post-intervention between-group benefits of MBIs relative to control conditions on primary symptom severity (Hedges $g = 20.59$, 95% CI = 20.12 to 21.06). Effects were demonstrated for depressive symptom severity (Hedges $g = 20.73$, 95% CI = 20.09 to 21.36), but not for anxiety symptom severity (Hedges $g = 20.55$, 95% CI = 0.09 to 21.18), for RCTs with an inactive control (Hedges $g = 21.03$, 95% CI = 20.40 to 21.66), but not where there was an active control (Hedges $g = 0.03$, 95% CI = 0.54 to 20.48) and effects were found for MBCT (Hedges $g = 20.39$, 95% CI = 20.15 to 20.63) but not for MBSR (Hedges $g = 20.75$, 95% CI = 0.31 to 21.81).
Kuyken et al. 2019	Meta-analysis	MBCT on depression relapse	9 RCTs; $N = 1258$, adults ages 18 and older	*Significant effect* of MBCT with reduction in risk of depressive relapse/recurrence over 60 weeks compared with usual care. Patients receiving MBCT had a reduced risk of depressive relapse within a 60-week follow-up period compared with those who did not receive MBCT (hazard ratio, 0.69; 95% CI, 0.58–0.82). Comparisons with active treatments suggest a reduced risk of depressive relapse within a

Table 2. (Continued)

Reference	Study design	Intervention	Study sample	Findings
				60-week follow-up period (hazard ratio, 0.79; 95% CI, 0.64–0.97).
Khoury et al. 2013	Meta-analysis	MBT for depression, anxiety	209 studies; $N = 12{,}145$, adults ages 18 and older	MBT effective in reducing anxiety and depression and did not differ from traditional CBT, behavioral therapies, and pharmacological treatments. Effect-size estimates suggested that MBT is moderately effective in pre-post comparisons ($n = 72$; Hedge's $g = 0.55$), in comparisons with waitlist controls ($n = 67$; Hedge's $g = 0.53$), and when compared with other active treatments ($n = 68$; Hedge's $g = 0.33$), including other psychological treatments ($n = 35$; Hedge's $g = 0.22$). MBT did not differ from traditional CBT or behavioral therapies ($n = 9$; Hedge's $g = -0.07$) or pharmacological treatments ($n = 3$; Hedge's $g = 0.13$).
Cramer et al. 2013	Meta-analysis	Yoga for depression	12 RCTs; $N = 619$, adults ages 18 and older	Moderate short-term effects of yoga on depression compared to usual care, relaxation, and aerobic exercise. Regarding severity of depression, there was moderate evidence for short-term effects of yoga compared to usual care (SMD = – 0.69; 95% CI – 0.99, – 0.39; $p < 0.001$), and limited evidence compared to relaxation (SMD = – 0.62; 95%CI – 1.03, – 0.22; $p = 0.003$), and aerobic exercise (SMD = – 0.59; 95% CI – 0.99, – 0.18; $p = 0.004$). Limited evidence was found for short-term effects of yoga on anxiety compared to relaxation (SMD = – 0.79; 95% CI – 1.3, – 0.26; $p = 0.004$).
Liu et al. 2015	Meta-analysis	Tai chi and qigong on depression	30 studies; $N = 2328$, adults ages 18 and older	*Significant effect* of Qigong interventions but *no effect* of Tai Chi for depression. A significant effect was found for the Qigong interventions (Cohen's *d* – 0.48 95% CI – 0.48 to – 0.12; SMG – 0.52, 95% CI – 0.79 to – 0.26). There was no significant effect seen

Table 2. (Continued)

Reference	Study design	Intervention	Study sample	Findings
				for tai chi (d – 0.07, 95% CI – 0.44 to 0.31).
Zou et al. 2018	Meta-analysis	Meditative movement (tai chi, qigong, and yoga) on depression	15 RCTs; $N = 844$, adults ages 18 and older	*Significant effect* of meditative movement on reducing depression severity compared to passive controls. Significant benefit in favor of meditative movement on depression severity (SMD = – 0.56, 95% CI – 0.76 to – 0.37, $p < 0.001$, $I^2 = 35.76\%$) and on anxiety severity (SMD = – 0.46, 95% CI – 0.71 to – 0.21, $p < 0.001$, $I^2 = 1.17\%$). Meditative movement interventions showed significantly improved treatment remission rate (OR = 6.7, 95% CI 2.38 to 18.86, $p < 0.001$) and response rate (OR = 5.2, 95% CI 1.73 to 15.59, $p < 0.001$) over passive controls.
Anxiety				
Hilton et al. 2017	Meta-analysis	Meditation interventions (MBSR, meditation, and yoga) on PTSD	10 RCTs; $N = 643$, adults ages 18 and older	*Significant effect* of meditative interventions on reducing PTSD symptoms. PTSD symptoms for adjunctive meditation interventions were statistically significantly different compared with all comparators (SMD 0.41; CI [0.81, 0.01]; 8 RCTs; I^2 67%) in favor of meditation.
Gallegos et al. 2017	Meta-analysis	Meditation and yoga on PTSD	19 RCTs; $N = 1173$, adults ages 18 and older	Possible *small effect* size of meditation and yoga on PTSD. A random effects model yielded a statistically significant ES in the small to medium range (ES = – 0.39, $p < 0.001$, 95% CI [– 0.57, – 0.22]).
Cramer et al. 2018	Meta-analysis	Yoga on PTSD	7 RCTs; $N = 289$, adults ages 18 and older	Low evidence for short term yoga on PTSD. Low quality evidence for clinically relevant effects of yoga on PTSD symptoms compared to no treatment (SMD = – 1.10, 95% CI [– 1.72, – 0.47], $p < 0.001$, $I^2 = 72\%$; MD = – 13.11, 95% CI [– 17.95, – 8.27])
Cognition				

Table 2. (Continued)

Reference	Study design	Intervention	Study sample	Findings
Berk et al. 2017	Systematic review	MBSR and MBCT for cognition	6 total studies with 3 RCTs; $N = 409$, adults ages 55 and older	Inconclusive differences of MBSR and active control group on several cognitive measures due to small sample size and studies
Wong et al. 2017	Longitudinal	mixed-methods observational study	Mindfulness training program on MCI	$N = 13$, adults ages 60 and older
Long-term	mindfulness practice associated with cognitive and functional	improvements for older adults with MCI after 1 year follow-up		
Farhang et al. 2019	Systematic review	MBIs (MBSR, MBCT, yoga, tai chi, meditative movements, qigong) on cognition impairment	9 RCTs; $N = 710$, adults ages 55 and older	MBIs improved cognitive function, everyday activities functioning, and mindfulness, as well as resulting in a moderate reduction in fall risk, depression and stress and lower risk of dementia at 1 year.
Zou et al. 2019	Meta-analysis	MBE (tai chi, yoga, qigong) on cognition	12 studies with 9 RCTs; $N = 1298$, adults ages 18 and older with MCI	*Significant effect* of MBE on improved attention, short-term memory, executive function, visual-spatial/executive function, and global cognitive function. MBE significantly improved attention (SMD = 0.39, 95% CI 0.07–0.71, $p = 0.02$, $I^2 = 31.6\%$, $n = 245$), short-term memory (SMD = 0.74, 95% CI 0.57–0.90, $p < 0.001$, $I^2 = 0\%$, $n = 861$), executive function (SMD = – 0.42, 95% CI – 0.63 to – 0.21, $p < 0.001$, $I^2 = 38.54\%$, $n = 701$), visual-spatial/executive function (SMD = 0.35, 95% CI 0.07–0.64, $p < 0.05$, $I^2 = 0\%$, $n = 285$), and global cognitive function (SMD = 0.36, 95% CI 0.2–0.52, $p < 0.001$, $I^2 = 15.12\%$, $n = 902$). Positive effect on cognitive processing speed was not observed following MBE interventions (SMD = 0.31, 95% CI – 0.01 to 0.63, $p = 0.054$, $I^2 = 28.66\%$, $n = 233$).

MBCT mindfulness-based cognitive therapy, *MBSR* mindfulness-based stress reduction, *MBIs* mindfulness-based interventions, *MBT* mindfulness-based therapy, *CBT* cognitive behavioral therapy, *MCI* mild cognitive impairment, *PTSD* post-traumatic stress disorder, *MBE* mind-body exercise

efficacy of mindfulness-based therapies on clinical vs. sub-clinical depression. Both pre-post studies and waitlist-controlled studies indicated a significant effect of mindfulness-based therapies targeting depressive symptoms [54]. Overall, there is consistent evidence demonstrating short and likely longer-term positive effects of mindfulness-based therapies on depression.

Anxiety disorders

Khoury and colleagues [55] investigated the efficacy of various standardized multicomponent mindfulness-based therapies (e.g., MBSR, MBCT) on clinical and sub-clinical anxiety [55]. Waitlist-controlled studies indicated a significant effect of mindfulness-based therapies targeting anxiety symptoms. Using the State-Trait Anxiety Inventory (STAI), sub-clinical anxiety was significantly reduced at post-treatment and follow-up. A moderate clinical baseline level of anxiety was reduced to a sub-clinical level post-treatment and to a mild level at follow-up. A high clinical baseline level of anxiety was reduced to moderate levels at both post-treatment and follow-up. The magnitude of these effect may be regarded as ranging from fairly small (mean = 6% improvement) for subclinical anxiety to more clinically significant for moderate and high levels of anxiety (18% and 11%, respectively). A more recent, larger meta-analysis of 10 RCTs from Hilton and colleagues showed significant improvement in PTSD symptoms with meditation interventions [56]. Similarly, another large meta-analysis including 19 RCTs by Gallegos et al. examining both meditation and yoga for PTSD showed a smaller effect size, while a meta analysis examining yoga alone on PTSD showed inconclusive results [57, 58]. This suggests the possibility that meditation rather than yoga may have a more significant effect on PTSD symptoms.

Cognitive disorders

A recent review by Berk et al. [59] reviewed six studies investigating the effects of MBTs on cognition in older adults. The studies reported a variety of neuropsychological tests to measure global cognitive function, executive function, and memory. Three of the six reviewed studies were RCTs, with most of the studies conducted as pilot projects and more appropriately interpreted as evidence of feasibility of MBI interventions in older adults. The review concluded that MBI for older adults were feasible, but results on cognitive improvement were inconclusive due a limited number of studies, small sample sizes, and a high risk of bias [59]. A more recent longitudinal mixed-methods observational study with a 1-year follow-up period using a customized 8-week group-based mindfulness training program for older adults with MCI (n = 14) showed significant improvements in cognitive function ($p < 0.05$) and trait mindfulness ($p < 0.05$) after completing the intervention in MCI participants. Those who meditated more during the 59 weeks

showed greater improvements in cognitive function ($p < 0.05$) and everyday activity functioning ($p < 0.05$), with large effect sizes at the 1-year follow-up [60]. Similarly, another review examined nine studies which indicated that mind-body interventions improved cognitive function, everyday activity functioning, and mindfulness, as well as resulting in a moderate reduction in fall risk, depression and stress, and lower risk of dementia at 1 year [61]. Inclusion criteria included more broad interventions such as mindfulness or meditation, yoga, tai chi, and qigong on cognitive function and everyday functionality of non-hospitalized adults aged 55 years or over with MCI. Although the data is promising, the conclusions are limited by number of studies and small sample size, heterogeneity of outcome measures, lack of an active control group, and absence of long-term follow up.

A growing body of research evidence supports the use of MBTs (including meditation, yoga, tai chi, and qigong) as minimally invasive, cost-effective approaches for the management of late-life mood and cognitive disorders. In contrast to pharmacological approaches, MBTs aim to teach patients life-long skills that may continue to confer benefits long after formal training has ended. Additional research evaluating the mechanisms by which MBTs improve mental health and cognition is needed. As the majority of studies to date have focused on younger and middle-aged adults, whether the proposed mechanisms by which MBTs improve mood, sleep, and well-being generalize to geriatric populations is less well understood. Improved understanding of the neurobiological mechanisms of MBTs will lead to the development of preventive interventions oriented toward promoting well-being and resilience in this vulnerable population.

Conclusion

Despite the increasing use of CIM by individuals and growing body of research examining the efficacy of CIM for treating mental disorders, research, and scientific support for its efficacy for older adults remains limited. Overall, there is stronger and more consistent evidence about the benefits of dietary interventions and mind-body therapies for mood and cognitive disorders, while the evidence for most herbal and nutritional supplements remains mixed and inconclusive. The non-invasive nature of mind-body therapies and Mediterranean diet modifications also make these CIM interventions more favorable over supplementation use due to the variability in formulations available, as well as potential drug-drug interactions. However, studies have consistently faced limitations, such as small sample size, heterogeneity of outcome measures, lack of an active control group, and absence of long-term follow-up, particularly in older adults. Additional research is needed to determine predictors and biomarkers of response that would allow identification of individuals who are more likely to respond to CIM. Implementing CIM

interventions in the communities will represent the next phase of CIM research as preventive, well-being oriented interventions for stress-diathesis disorders.

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