

Integrative Medicine for Treating Depression: An Update on the Latest Evidence

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Abstract Integrative medicine (IntM) is a growing medical trend combining conventional medical approaches with evidence-based complementary therapies to promote well-being. Over half of individuals with depression use some form of IntM for symptom management. The purpose of the current study was to critically review the scientific evidence for IntM techniques in treating adult unipolar depression. We examined randomized controlled trials, systematic reviews, and meta-analyses published in the last one to three years using PsychINFO, PubMed, and Cochrane Library databases. The strongest evidence currently exists for mindfulness-based interventions and St. John's Wort (SJW) as monotherapies, and there is relatively strong evidence to support the use of omega-3 fatty acids and exercise as adjunct therapies. However, there remains an overall lack of methodologically rigorous research to support the efficacy of many other IntM techniques. Providers should be aware that many patients use IntM techniques for depression treatment and inquire regularly about such use.

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Introduction

Major depressive disorder (MDD) is a highly prevalent chronic illness that will affect 10-20 % of the United States (US) population during their lifetime [1]. Depression consistently ranks as a top cause of disability worldwide and is associated with significant economic healthcare costs [2]. As defined by the fifth edition of the Diagnostic and Statistical Manual (DSM-5), MDD involves a depressed mood or loss of pleasure in activities plus four other criteria (e.g., change in sleep, energy, concentration, appetite) over the same two week period [3]. Evidence-based first-line treatments for depression include psychotherapy, particularly Cognitive-Behavioral Therapy (CBT), or pharmacologic agents, though the greatest improvements are shown with the combination of these approaches [4]. Pharmacologic treatment typically commences with the selective serotonin reuptake inhibitors (SSRIs) given their relative low cost and good safety profiles; however, gastrointestinal disturbance and sexual dysfunction side effects often lead patients to discontinue treatment [5]. Alternative antidepressant options include tricyclic antidepressants, though these medications have greater anticholinergic side effects and can be fatal in overdose, and serotonin and norepinephrine reuptake inhibitors, which are often initiated after at least one SSRI trial. Across all medications, patients require close monitoring for the possible development of manic symptoms or worsening suicidal ideation.

Integrative medicine (IntM) is a holistic approach to health and healing that combines conventional medicine with safe and effective complementary and alternative medicine (CAM) techniques [6]. Integrative medicine is patient-centered and personalized, addressing all physical, emotional, psychological, social, spiritual, and environmental factors that influence a patients' unique state of health [7]. Core tenants of an IntM philosophy include: a focus on the patient-provider relationship; engaging mind, body, spirit, and community to optimize an innate healing response; and the belief that healing is always possible - even if curing is not [6]. The National Center for Complementary and Alternative Medicine (NCCAM) identifies four categories of CAM modalities: 1) mind-body medicine (e.g., yoga, acupuncture), 2) natural products (e.g., herbs, supplements), 3) manipulative and body-based practices (e.g., chiropractic, massage), and "other" CAM practices (e.g., energy therapies, whole medical systems [8]). However, what is considered CAM is constantly changing, as the evidence base for certain techniques grows and the technique becomes adopted into mainstream medicine.

Integrative medicine is an expansive and growing medical trend [9], primarily driven by consumer demand. In two nationally representative samples of over 22,000 healthy adults and 2000 adults with depression, approximately 40 % and 54 %, respectively, reported using some form of IntM in the past year, most commonly natural products and mind-body medicine [1, 10]. Common reasons for IntM use include relieving illness symptoms and side effects of conventional medicine treatments, increasing a sense of control over one's own health, and improving overall well-being [10].

A large and growing body of evidence supports the use of IntM for many chronic conditions including depression [6]. In 2002, a thorough review of 37 IntM techniques for treating depression concluded that the strongest evidence at that time existed for St. John's wort (SJW) and exercise; that there was limited evidence for many other modalities (e.g., acupuncture, massage therapy); and that no IntM modalities were as empirically well-supported as antidepressants or Cognitive Behavioral Therapy (CBT [11]). A 2011 review of select IntM techniques reaffirmed that SJW and exercise were effective for treating depression, acupuncture was ineffective, and several other therapies were promising and warranted further study [12]. There have been a number of additional studies since that time, and a number of IntM techniques that have not been recently reviewed (e.g., mindfulness meditation, yoga). The purpose of the current review was therefore to provide an update of the latest evidence for IntM techniques in treating adult depression.

Method

We conducted a comprehensive literature review of a range of IntM techniques for the treatment of unipolar depression

published in the last one to three years using PsychINFO, PubMed, and Cochrane Library databases. Studies prior to the last three years were mentioned only if they were the most recent rigorous study in the area. Search terms included *depression* and *integrative medicine*, *complementary medicine*, *alternative medicine*, and specific IntM modalities (e.g., *yoga*, *massage*, *St. John's Wort*, *exercise*, *reiki*). We focused our search on natural products on herbal therapies and supplements most commonly studied in depression (e.g., *St. John's Wort*). We did not conduct an exhaustive, systematic review of all literature in these areas given the scope of this paper; rather, we focused specifically on higher-quality randomized controlled trials, systematic reviews, and meta-analyses. We included studies focused on adults with a primary diagnosis of major depressive disorder (MDD), or elevated levels of depressive symptoms. We included studies of depression alongside other emotional disorders (e.g., anxiety) only if subgroup analyses were presented by disorder, or if they were the only recent studies of that IntM modality. We did not include studies of children or adolescents, or studies in which depression presented as secondary to a comorbid medical condition. Dissertations and non-English manuscripts were also excluded. Results are presented by NCCAM categories with specific subcategories for each, and summarized in Table 1.

Results

Mind-Body Medicine

Mind-body medicine is defined as a set of techniques that aim to unite the body and mind in order to promote health and well-being (e.g., yoga, meditation, relaxation strategies [8]).

Mindfulness-Based Interventions

Recent research on meditation for depression has focused almost exclusively on mindfulness meditation, a form of insight meditation originating in Buddhist traditions. Research has focused primarily on Mindfulness-Based Cognitive Therapy (MBCT [13]), and secondarily on Mindfulness-Based Stress Reduction (MBSR; [14]). MBCT is an 8-week program designed to prevent depressive relapse by loosening the association between negative thoughts and negative mood, and increasing conscious awareness of moment-to-moment changes in body sensations, emotional states, and thought patterns using mindfulness meditation-based techniques (e.g., mindful breathing, body scan). This process allows patients to notice the oncoming signs of depression and pro-actively engage in activities to prevent downward mood spirals. MBSR is an 8-week manualized intervention originally designed for chronic pain patients, which similarly aims to extinguish maladaptive responses to difficult events by promoting more adaptive and goal-directed behavior.

Table 1 Summary of recent studies of integrative medicine techniques for treating depression

Integrative medicine technique	Number & type of included studies	Approximate number of unique original studies	Quality of evidence	Primary findings	Effect size	Clinical implications
Mindfulness-based interventions ^a	2 reviews [15, 16] 3 meta-analyses [17–19]	17	Relatively high; low risk of bias	Effective and comparable to standard treatment for depression treatment and relapse prevention	$g=.95$ $d=.83$ Reduced Risk=34 %	Recommend as monotherapy or adjunct
Relaxation	1 pilot study [25]	1	Poor	Promising reductions in depressive symptoms	–	Consider as adjunct
Yoga	2 reviews [26, 27] 1 RCT [28]	11	Poor	Promising but methodological flaws	$d=.17$	Consider as adjunct
Acupuncture	6 reviews [29, 30, 31*, 32–34]	68	Relatively low; high risk of bias	Safe, popular, promising but insufficient due to poor methodological quality	–	Insufficient evidence for recommendation
Tai Chi	2 pilot studies [36, 37]	2	Poor	Promising reductions in depressive symptoms	–	Insufficient evidence for recommendation
St. John's Wort	1 review [38] 1 re-analysis of earlier data [39]	19	Relatively high	Effective and comparable to standard treatment for mild to moderate depression	$d=.64$	Recommend as monotherapy or adjunct for mild to moderate depression
SAM-e	2 reviews [38, 40]	16	Poor	Promising reductions in depressive symptoms	Moderate: $d=1.0$ Severe: $d=.87$	Insufficient evidence for recommendation
Folate	2 reviews [41, 42]	10	Poor	Consistent association, promising reductions in depressive symptoms	–	Consider as adjunct
Vitamin D	1 review [45] 2 RCTs [46, 47]	4	Poor	Very preliminary promising reductions in depressive symptoms as adjunctive treatment	–	Insufficient evidence for recommendation
Omega-3 fatty acids	2 meta-analyses [48, 49] 1 RCT [50]	14	Relatively high	Small reductions in depressive symptoms as an adjunctive treatment	SMD=.23	Consider as adjunct
Exercise	2 reviews [52, 53] 3 meta-analyses [54, 55**, 56]	53	Generally moderate	Small reductions in depressive symptoms as adjunctive treatment	SMD=-.31	Consider as adjunct; encourage preferred mode of exercise
Traditional Chinese Medicine	1 review [60] 1 meta-analysis [59] 1 non-RCT [58]	23	Poor	Promising reductions in depressive symptoms	–	Insufficient evidence for recommendation

Note. g =Hedge's g ; RCT=randomized controlled trial; d =Cohen's d ; SAM-e=S-Adenosyl Methionine; SMD=standardized mean difference

^a Mindfulness-Based Cognitive Therapy and Mindfulness-Based Stress Reduction

Several systematic reviews [15, 16] and meta-analyses [17–19] suggest that mindfulness-based interventions are effective and quite promising treatments for depression. Results indicate fairly large effect sizes for reducing depressive symptoms ($g=.95$) and relapse rates (reduced risk=34 %), with effects maintained up to one year later, and no significant differences between mindfulness-based interventions and antidepressants or CBT [15, 17, 18, 20]. For example, patients who achieved unstable remission after treatment with antidepressants showed significantly reduced and equivalent relapse rates when subsequently treated with MBCT (28 %) or antidepressants (27 %), as compared to placebo (71 % [21••]). Importantly, the quality of these studies is determined to be relatively high, with no evidence of publication bias or heterogeneity between studies, and the use of well-validated active control groups [17, 18]. Further research regarding dosing and mechanisms for mindfulness-based interventions is warranted [16].

One important development in this area is whether or not MBCT is more effective at preventing depressive relapse for individuals with a greater number of past depressive episodes. According to MBCT theory and preliminary research, patients with a history of three or more depressive episodes should show the greatest treatment response, as there is presumably a stronger link to be broken between negative thoughts and negative mood [22]. Although most research supports this idea [15], emerging research suggests that MBCT is effective regardless of severity of depression history [20, 23].

Case Study: MBCT for Depression

Debbie, a 37-year-old Appalachian female, struggled with depression for most of her life subsequent to a traumatic childhood. MBCT was informally adapted for use with Debbie in individual psychotherapy. Initially, Debbie was keenly aware of her depressive thinking patterns, such as “Nobody cares about me,” and “I can’t do anything right.” Cognitive-behavioral therapy traditionally encourages patients to challenge the rationality of such thoughts directly; however, Debbie’s mind was quick to counter her own counter-thoughts. Through mindfulness practice, Debbie was taught to de-center from such thoughts. That is, rather than answer the thoughts, she learned the meta-cognitive skill of making observations such as, “I’m noticing that I’m arguing with myself about my self-worth. That must mean I’m getting depressed. I’d better go do some physical activity to pull myself out of it.” After several weeks of practice, Debbie increasingly noticed her thinking patterns before they became too entrenched, and found that she was better able to pull herself out of a sad mood before it led to the withdrawal behaviors that precede depressive episodes.

Relaxation Techniques

Relatively little research has focused on relaxation interventions for depression in recent years. A 2009 Cochrane review of 15 randomized or quasi-randomized controlled trials of progressive muscle relaxation, guided imagery, and autogenic training (i.e., imagined sensations of warmth, heaviness, and relaxation in the body) concluded that relaxation treatments are more effective than no treatment or minimal treatment, but not as effective as psychotherapy (i.e., CBT) for reducing depressive symptoms [24]. We only identified one study of relaxation for depression since that time. This study compared an 8-week relaxation training to CBT among 133 young adults with elevated depressive symptoms, but no history of depression, and found clinically and statistically significant improvements among both groups over a six-month period ($p<.001$ [25]). Participants in the CBT group demonstrated a larger immediate improvement ($d=1.32$) than the relaxation group ($d=.66$), but the effects of CBT diminished over time, whereas the effects of relaxation steadily improved. These findings should be interpreted with caution given the lack of a no-treatment or placebo control group.

Yoga

We identified two recent reviews of yoga specifically for depression [26, 27]. These reviews both conclude that yoga is feasible for adults with depression, and there are some promising preliminary results to support its efficacy; however, significant methodological flaws and heterogeneity between yoga protocols prevent definitive conclusions. Specifically, four out of five RCTs found that yoga was superior to no treatment and some active treatments (e.g., psychoeducation, progressive muscle relaxation; $d=.17$ to $.16$); however, active control groups were not always matched for time or other non-specific factors, and outcome raters were often not blind to treatment group, which limits the strength of these findings [26]. In a recent small mixed-methods study, yoga significantly reduced depressive symptoms to the same extent as a health education control; subjective reasons for improvement differed, however, in that only the yoga group reported learning a new coping strategy [28]. Further research on mechanisms, as well as safety and dosing of yoga interventions, is needed.

Acupuncture

We identified six systematic reviews of acupuncture for depression in the last three years [29, 30, 31•, 32–34]. Most reviews, including a Cochrane review of 30 studies [31•], concluded that although acupuncture is popular and appears to be safe, there remains insufficient evidence to recommend acupuncture for depression treatment due to a high risk of bias and significant methodological limitations (e.g., heterogeneity

between acupuncture protocols, small sample sizes). While a review of the 20 most high-quality studies concluded that the effects of acupuncture are comparable to those of antidepressants, and acupuncture was associated with fewer adverse events, these studies continue to suffer from significant methodological limitations. Additionally, some studies show no difference between acupuncture and sham acupuncture, and it remains unclear how acupuncture augments the effects of antidepressants [30, 32]. Important barriers to acupuncture research include the overrepresentation of Chinese-language studies, which generally report more favorable results than studies from the United States [33, 34], and the use of adequate control groups and issues of blinding. To allow for a double-blind design, one recent study compared laser acupuncture to placebo acupuncture (i.e., same procedure with no laser beam released [35]). Results indicated clinically and statistically significant reductions in depressive symptoms (HAM-D decrease=11.74) and a greater number of remitted patients in the laser acupuncture group (64 % vs. 5 %, respectively). Thus, there remains some promising but largely insufficient evidence to support the use of acupuncture for depression.

Tai Chi

There have been two recent pilot RCTs of tai chi for depression. First, 73 elderly adults with depression who did not respond to treatment with antidepressants were randomly assigned to a 10-week tai chi intervention or health education control group [36]. The tai chi group reported greater improvements in depressive symptoms ($p < .05$), and a greater number of participants achieved remission in the tai chi group as compared to the control group, though the differences were not statistically significant (65 % vs. 51 %, respectively; $p < .06$). The attrition rate was low (7 %) and no adverse events were reported. Results of this study are encouraging, as it utilized blind outcome raters, an active control matched for time and attention, and well-validated outcome measures.

Yueng and colleagues (2012 [37]) conducted a 12-week RCT of tai chi, as compared to a wait-list control, as an adjunct to antidepressants for 39 Chinese Americans with depression. There were no adverse events, a relatively low attrition rate (27 %), greater response rates in the tai chi group as compared to the control group (24 % vs. 0 %, respectively), and improved remission rates in the tai chi group as compared to the control group (19 % vs. 0 %, respectively). However, because this pilot study was significantly underpowered, these differences were not statistically significant. The lack of an active control group also limits the ability to draw definitive conclusions.

Summary of Mind-Body Medicine for Depression

The strongest current evidence from relatively high quality studies is for the efficacy of mindfulness-based interventions,

particularly MBCT, for reducing depressive symptoms and preventing relapse. While there is some promising evidence for the efficacy of relaxation, yoga, acupuncture, and tai chi for depression, the relatively poor methodological quality of these studies limits the ability to draw definitive conclusions. Future RCTs should examine the effectiveness of these mind-body interventions for depression using appropriate, standardized treatment protocols and depression diagnoses, blind outcome raters, larger sample sizes, and active control groups. Further research is also needed to examine the safety, optimal dosing, and mechanisms of action for these treatments.

Natural Products

Natural products include biologically-based substances intended to promote overall health, including herbal medicines or botanicals (e.g., St. John's Wort), vitamins and minerals, and other dietary supplements (e.g., probiotics). These modalities may be used either in supplement form or as part of a whole-foods diet.

Herbs and Botanicals

St. John's Wort St. John's Wort (SJW; *Hypericum perforatum*) is a flowering plant with a long history of medicinal use. Extant research suggests that SJW is more effective than placebo, comparable to antidepressants, and has fewer side effects than antidepressants. For example, one recent systematic review of 17 double-blind, sufficiently-powered (i.e., $N \geq 40$) RCTs found that SJW as monotherapy was superior to placebo and comparable to antidepressants in reducing short-term (e.g., 4-12 weeks) depressive symptoms for patients with mild to moderate, but not severe, depression ($d = .26$ to 1.83 ; $M_d = .64$), though it was not associated with long-term improvements [38]. St. John's Wort appears to be relatively safe, with the risk of adverse events, most commonly abdominal pain, nausea, and diarrhea, being similar to placebo and lower than antidepressants; the highest risk occurs in combination with Paroxetine [39]. Few studies of SJW have reported increased depressive symptoms and none reported increased suicidal ideation or behavior; however, many studies of SJW do not report on adverse events at all, which is a significant limitation of research in this area [38].

Vitamins, Minerals, and Supplements

S-Adenosyl Methionine (SAM-e) SAM-e is a naturally occurring physiological substance composed of adenosine triphosphate and methionine that is involved in important biochemical pathways of the central nervous system [38]. In a recent systematic review, SAM-e as monotherapy for depression showed significant effects as compared to placebo, with fairly large effect sizes for moderate depression ($d = .33$ to 1.6 ;

$M_d=1.0$), as well as for severe depression ($M_d=.87$ [38]). A recent review concluded that SAM-e was one of only two supplements (along with omega-3) with sufficient evidence of safety and effectiveness [40]. However, all double-blind studies of SAM-e for depression are reported to be of poor methodological quality, thus limiting the strength of these conclusions [38].

Folate

There is a consistent association between low folate levels and depression, and some evidence that folate is effective as an adjunct to antidepressants, particularly for those with low folic acid levels [41, 42]. Additionally, low folic acid is associated with poor response to antidepressants and, thus, folic acid augmentation is thought to enhance antidepressant treatment response [42]. However, few of these studies have been double-blind, placebo-controlled trials, making results less conclusive [42]. Recently, attention has focused on the importance of L-methyl folate in depressive disorders, as folate itself is biologically inactive and must be converted into L-methyl folate in order to cross the blood-brain barrier and facilitate neurotransmitter synthesis [43]. The FDA has recently approved L-methyl folate supplements in the form of prescription medical foods intended to improve folate levels and antidepressant response in depressed patients. Preliminary research suggests that these supplements are safe and promising adjuncts to antidepressants [43]. We found no evidence that folate is effective as monotherapy [41].

Vitamin D

Most research on vitamin D and depression involves cross-sectional or epidemiological studies, and most controlled studies have focused on seasonal affective disorder, utilized healthy participants, or have significant methodological flaws (e.g., inactive control group [44–46]). Overall, the current evidence does not definitively support vitamin D as a causal or risk factor, or as an effective treatment for depression due to poor research methodologies. We identified only one double-blind RCT of vitamin D augmentation, which found that fluoxetine augmentation with vitamin D was associated with significantly fewer depressive symptoms than fluoxetine alone [47].

Omega-3 Fatty Acids

A meta-analysis of 13 randomized, placebo-controlled studies concluded that the effects of omega-3 s were greater for more severe depression, but generally small and insignificant [48]; however, a re-analysis of this data focusing only on individuals with DSM-diagnosed depression found that omega-3 s were associated with a significant antidepressant effect

($SMD=.23$, 95 % $CI=.05-.24$, $p=.01$ [49]). This study also found that the dose and composition of omega-3 supplementation is important, with supplements with greater than 60 % eicosapentaenoic acid (EPA) being associated with the greatest symptom reductions [49]. Treatment effects were similar for omega-3 s as monotherapy or as an adjunct to standard treatment [48, 49]. Results from the largest double-blind RCT to date ($N=432$) found that omega-3 supplementation was associated with greater depressive symptom reductions than placebo only among individuals without comorbid anxiety symptoms [50].

Case Study: Supplements for Depression

Jack, a 41 year-old male with a history of depression, presented for treatment at the request of his fiancé. He was physically healthy overall despite being overweight, and was currently working with his primary care physician to implement a diet and exercise weight loss regimen. A clinical assessment using the Patient Health Questionnaire (PHQ-9) at the start of the current treatment indicated a diagnosis of major depression (PHQ-9=14), which was confirmed by clinical exam, and Jack was provided information about the full range of treatment options from dietary supplements to SSRI's. Jack quickly expressed his resistance to pharmacological treatments, stating that he doesn't "want a bunch of pills that make [him] feel like some sort of zombie." Given his aversion to medication, relatively mild symptoms, lack of suicidal ideation, recent focus on lifestyle modification, and close ongoing relationship with his therapist, the shared decision making process resulted in a trial of both omega-3 fish oil and SAM-e supplements. Jack reported relief that he was not prescribed antidepressants, and he began taking both supplements. Three weeks later, he discontinued the fish oil due to belching and an uncomfortable aftertaste, though he tolerated the SAM-e well and only complained about the high cost. He was advised to increase his dosage to 400 mg/day and continue with psychotherapy. Six weeks later, Jack's affect was notably improved, he reported increased energy, and his PHQ-9 score indicated remission of his depressive symptoms (PHQ-9=4).

Summary of Natural Products for Depression

Research on natural products for depression is currently the strongest for SJW and omega-3 fatty acids. Several well-designed studies of SJW suggest that it is safe and as effective as antidepressants for the treatment of mild to moderate depression. Omega-3 fatty acids, particularly supplements with greater than 60 % EPA, appear to have a significant antidepressant effect for patients with more severe DSM-diagnosed depression, but they may not be effective for those with subclinical depressive symptoms or other psychological comorbidities.

Although there is some encouraging evidence for the efficacy of folate, SAM-e, and vitamin D, definitive conclusions cannot be drawn at this time due to the low number and/or quality of existing studies.

Manipulative and Body-Based Techniques

Manipulative and body-based techniques, such as chiropractic, osteopathy, and massage therapy, aim to affect bodily systems in a way that enhances well-being [8]. We did not identify any studies of chiropractic or osteopathy for depression, or any recent studies of massage therapy for depression. Previous reviews of massage therapy for depression found insufficient evidence of efficacy [51]. Thus, evidence for the use of manipulative and body-based techniques for depression is currently lacking.

Other IntM Techniques

Integrative medicine techniques that do not fit neatly into the aforementioned categories include movement therapies (e.g., Pilates, the Alexander Technique), traditional healers, energy therapy (e.g., reiki, healing touch), and traditional whole medical systems (e.g., Ayurveda, Traditional Chinese Medicine). Given the wide use of exercise for depression treatment, particularly in combination with conventional pharmacotherapy, we have included exercise as an IntM movement therapy in the current review.

Movement Therapies: Exercise

There have been several recent systematic reviews [52, 53] and meta-analyses [54, 55•, 56] of exercise for depression. Recent findings, including results of a Cochrane review, suggest that exercise as monotherapy shows a moderate effect size as compared to no-treatment or placebo controls (SMD=-.67); is comparable to antidepressants, CBT, and other forms of physical activity; and may be beneficial as an adjunct to usual care [53, 54, 55•]. However, effect sizes are reduced in higher-quality studies (SMD=-.31 [55•]). Many public health guidelines, as well as the American Psychiatric Association, recommend exercise as an adjunctive treatment for depression and, given its comparable benefits to other forms of physical activity, suggest that providers tailor exercise prescriptions to the individual's activity level and preferred type of activity as a way of increasing motivation [52, 57].

Whole Medical Systems: Traditional Chinese Medicine (TCM)

Most research on TCM for depression has focused on the use of Chinese herbs. In one recent non-randomized pilot study of acupuncture alone compared to acupuncture with Chinese

herbs, participants in both groups reported significant decreases in depressive symptoms, which were maintained over a three month period ($p < .001$); however, there were no significant differences between groups ($p = .52$), indicating no incremental benefit of Chinese herbs in treating depression [58]. A meta-analysis of ten RCTs comparing antidepressant augmentation with the TCM formula Chaihu-Shugan-San (CSS) to antidepressants alone found that all studies reported significantly fewer depressive symptoms and an increased recovery rate for CSS augmentation, and no adverse events were reported (OR=2.32, 95 % CI=1.61 to 3.34 [59]). However, all studies were methodologically poor (Jadad \leq 3) and at high risk of bias [59]. Another systematic review similarly found that Chinese herbs, particularly Xiao Yao San, were more effective than placebo and comparable to antidepressants, but the studies were of poor methodological quality due to issues of blinding and variation in the constitution of different herbal formulas [60]. High quality research on the safety of TCM herbs and their interactions with antidepressants is lacking.

Conclusion

There has been significant research attention focused on IntM techniques for treating depression in recent years. Overall, the strongest evidence currently exists for mindfulness-based interventions and St. John's Wort; there is fairly strong evidence for omega-3 fatty acids and exercise; and the evidence for many other techniques is promising, but inconclusive due to the number and/or quality of existing studies.

Mindfulness-based interventions and SJW both demonstrate efficacy as monotherapy, even when compared to current gold-standard treatments. Both techniques show relatively large effect sizes, though mindfulness-based interventions appear to be effective for varying presentations of depression, whereas SJW is most effective for mild to moderate depression. Omega-3 fatty acids and exercise show small effect sizes and appear to be most effective as adjunctive, rather than monotherapies. The current findings differ from earlier reviews, which found strongest evidence to support the efficacy of SJW and exercise, but concluded that neither was as effective as standard treatments [11, 12].

Though promising, there remains an overall lack of methodologically rigorous research supporting the efficacy of relaxation, yoga, acupuncture, SAM-e, tai chi, folate, and vitamin D for the treatment of adult depression. Further research is needed on the efficacy of these techniques; the safety, dosing, and mechanisms of all IntM techniques; and the comparative effectiveness of different IntM techniques (and in various combinations) for treating depression. Future studies should aim to include larger sample sizes; standardized IntM protocols, selection criteria, and validated outcome measures; longer follow-ups; active control

groups; adequate reporting of randomization methods; and blind outcome raters. Providers should be aware that many patients use IntM techniques for depression treatment and inquire regularly about such use.

Compliance with Ethics Guidelines

Conflict of Interest Christina M. Luberto, Christopher White, Richard W. Sears, and Sian Cotton declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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