Complementary and Alternative Medicine in Major Depressive Disorder: The American Psychiatric Association Task Force Report

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Objective: To review selected complementary and alternative medicine (CAM) treatments for major depressive disorder (MDD).

Participants: Authors of this report were invited participants in the American Psychiatric Association's Task Force on Complementary and Alternative Medicine.

Evidence: The group reviewed the literature on individual CAM treatments for MDD, methodological considerations, and future directions for CAM in psychiatry. Individual CAM treatments were reviewed with regard to efficacy in MDD, as well as risks and benefits. Literature searches included MEDLINE and PsycINFO reviews and manual reference searches; electronic searches were limited to English-language publications from 1965 to January 2010 (but manual searches were not restricted by language). Treatments were selected for this review on the basis of (1) published randomized controlled trials in MDD and (2) widespread use with important clinical safety or public health significance relevant to psychiatric practice. An action plan is presented based on needs pertaining to CAM and psychiatry.

Consensus Process: Consensus was reached by group conferences. Written iterations were drafted and sent out among group members prior to discussion, resolution of any differences of interpretation of evidence, and final approval.

Conclusions: A review of randomized controlled trials for commonly used CAM treatments such as omega-3 fatty acids, St John's wort (*Hypericum*), folate, S-adenosyl-L-methionine (SAMe), acupuncture, light therapy, exercise, and mindfulness psychotherapies revealed promising results. More rigorous and larger studies are recommended. Each CAM treatment must be evaluated separately in adequately powered controlled trials. At this time, several CAM treatments appear promising and deserve further study. The greatest risk of pursuing a CAM therapy is the possible delay of other well-established treatments. Clinical, research, and educational initiatives designed to focus on CAM in psychiatry are clearly warranted due to the widespread use of CAM therapies.

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Complementary and alternative medicine (CAM) has been defined as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine."[1]

Complementary refers to approaches that are not considered mainstream or conventional, but are consistent with Western biomedical concepts. *Alternative* approaches are considered outside of traditional Western medical concepts. *Integrative* medicine refers to the combination of CAM and conventional treatments with the goal of achieving the best clinical outcomes for patients.

Many CAM treatments are commonly used and readily accessible, though few have received adequate study for psychiatric conditions. Approximately 40% of US adults use at least 1 CAM therapy annually.[2] Many individuals with psychiatric disorders turn to CAM either as an adjunct to or in lieu of conventional therapies. In a survey of CAM utilization, approximately 10% of US adults surveyed who had visited a CAM provider had a self-reported psychiatric diagnosis, and approximately half of those had sought care from a CAM provider specifically for a psychiatric indication.[3] Simon et al[4] assessed visits to CAM providers and found 11% of visits were sought for mental health conditions. In a survey of a nationally representative US sample, Kessler et al[5] found that over half of respondents with self-reported depression or anxiety disorders used CAM therapies, and the majority of those using CAM treatments were also receiving treatment from conventional health care providers. In a study of patients hospitalized for psychiatric indications, 63% reported having used a CAM therapy within the past year.[6] Major depressive disorder (MDD) was the most common diagnosis associated with CAM use, and, importantly, 79% had not disclosed CAM use to their psychiatrist. Unützer et al[7] demonstrated that individuals with diagnoses of MDD were significantly more likely than those without MDD to use CAM therapies. The widespread use of CAM treatments and the common use of CAM for highly prevalent mental illnesses make it essential that psychiatrists understand the benefits and risks of CAM.

METHOD

Overview

Authors were appointed participants of the American Psychiatric Association's Task Force on Complementary and Alternative Medicine. The Task Force selected specific CAM treatments for a final report based on CAM utilization rates, relevance to the treatment of MDD, and public health significance.

Objectives

(1) The evidence regarding commonly utilized CAM treatments for MDD with available data from randomized controlled trials (RCTs) was evaluated. Efficacy, risks, side effects, drug interactions, and general health implications were reviewed. (2) Clinical, research, and educational needs regarding CAM in psychiatry were identified.

Search and Selection Methods

Individual CAM treatments were reviewed with regard to efficacy in MDD, as well as risks. Literature searches included MEDLINE and PsycINFO reviews and manual reference searches. Electronic searches were limited to English-language publications from 1965 to January 2010 (although manual searches included other languages). Keywords used were *major depressive disorder, CAM, complementary, alternative, psychiatry, omega-3, S-adenosyl-L-methionine, exercise, psychotherapy, mindfulness, folate, methylfolate, Hypericum, St John's wort, integrative, light therapy,* and *bright light.* We selected treatments for this review on the basis of (1) the presence of randomized controlled trials in MDD and (2) widespread use with important clinical safety or public health significance relevant to psychiatric practice.

Consensus Process

Consensus was reached by group conferences. Written iterations were drafted and sent out among group members prior to discussion, resolution of any differences of interpretation of evidence, and final approval.

RESULTS

CAM Therapies for the Treatment of MDD

Omega-3 fatty acids. Omega-3 fatty acids are polyunsaturated fatty acids with widely established health benefits. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are long-chain omega-3 fatty acids found in fish and marine sources. The typical American diet is relatively deficient in omega-3 fatty acids, compared to omega-6 fatty acids and other dietary fats.[8] The cardiovascular benefits of omega-3 fatty acids include decreased risk of thrombosis and arrhythmias, reduction of triglyceride levels in hypertriglyceridemia, decreased atherosclerosis, reduced inflammation, and modest improvement in hypertension.[9] Epidemiologic studies have supported a role for omega-3 fatty acid consumption in mood disorders. In cross-national analyses, inverse associations have been demonstrated between per capita fish intake and prevalence rates of major depression, postpartum depression, and bipolar disorder.[10,11]

Meta-analyses of omega-3 fatty acids for the treatment of mood disorders demonstrate benefits in placebo-controlled trials of unipolar and bipolar depression,[10–12] although heterogeneity of study designs and results has been noted as a methodological concern. Studies vary in terms of omega-3 fatty acids used, doses, and durations of trials. Most RCTs have included small numbers of patients who had MDD despite treatment with an antidepressant, with omega-3 fatty acids added as adjunctive treatment. Peet and Horrobin[13] demonstrated a benefit of 1 g/d in an RCT (N=70) of 1, 2, or 4 g/d versus placebo in patients with MDD. Nemets et al[14] also found EPA 2 g/d to be more efficacious than placebo in decreasing symptoms of depression in MDD (N=20). Su et al[15] and Silvers et al[16] used combinations of EPA and DHA in patients with MDD with differing results. Su et al demonstrated a benefit of EPA and DHA over placebo (N=28),[15] while Silvers et al did not find a difference between omega-3 and placebo groups (N=77).[16] A recent trial[17] of omega-3 fatty acids adjunctive to antidepressants did not show a benefit over placebo, although unlike most studies that used a combination of EPA and DHA, the DHA dose was higher than the EPA dose.

Most placebo-controlled studies conducted to date in MDD have been adjunctive studies. A few studies have assessed omega-3 fatty acids as a monotherapy. In one study, DHA (2 g/d) for MDD in 36 adults was not significantly more efficacious than placebo.[18] In another small monotherapy trial of EPA for MDD (N=57), investigators observed a trend toward efficacy ($P=.087$) for EPA 1 g/d compared to placebo, with response on the Hamilton Depression Rating Scale (HDRS) as the primary outcome.[19] One trial in children demonstrated a benefit of omega-3 fatty acid monotherapy (EPA and DHA) compared with placebo.[20] In another recent study, investigators assessed omega-3 fatty acids (EPA 1 g/d) versus fluoxetine 20 mg/d versus the combination of the 2 for MDD in 60 patients.[21] EPA and fluoxetine had similar efficacy, with the combination superior to either alone. Positive studies of omega-3 fatty acid in mood disorders have generally shown efficacy for treatment with EPA alone or EPA and DHA in combination (with EPA present in greater doses than DHA). Omega-3 fatty acids have received specific study in perinatal depression. Small RCTs of omega-3 fatty acids (26–59 subjects per trial) have resulted in mixed findings in pregnant and postpartum women with MDD.[22]

Side effects of the recommended doses of omega-3 fatty acids in MDD are relatively minor and include mild gastrointestinal discomfort, most commonly burping or unpleasant taste. Although increased bleeding is a theoretical risk, no actual cases of bleeding have been reported, even though there have been high-dose trials in which patients were medically compromised, postoperative, and/or using concomitant anticoagulants. However, a case was reported in which a patient treated with warfarin experienced significant changes in coagulation studies (but no clinical changes) after an increase in dose of fish oil.[23]

Doses of 1 to 9 g/d of omega-3 fatty acids have been studied in mood disorders, with a majority of evidence supporting doses in the lower end of this range. A dose-finding study[24] using 3 doses of DHA monotherapy demonstrated greater efficacy at 1 g/d compared to 2 g/d and 4 g/d, consistent with the findings of an RCT of ethyl-EPA as adjunctive treatment in MDD that showed greater benefit at lower doses.[13] Adjunctive EPA or the combination of EPA and DHA appear most useful, with less evidence for DHA alone. The established general health benefits of omega-3 fatty acids, epidemiologic

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evidence, modest efficacy data, and low risks make omega-3 fatty acids a reasonable augmentation strategy in MDD.

***St John's wort* (Hypericum).** St John's wort is an herbal remedy widely used in Europe. A large number of placebo-controlled or active comparator trials assessing St John's wort (usually in the form of *Hypericum perforatum* extract) have been published. However, a lack of a consensus on efficacy for MDD has resulted. A Cochrane meta-analysis assessed studies utilizing St John's wort for the treatment of MDD, but found heterogeneity in methodology and inconsistency in outcomes.[25] A number of double-blind studies have demonstrated superiority over placebo, although others have not.[26,27] Additionally, several randomized studies have failed to demonstrate statistically significant differences between approved antidepressant medications, and data support that St John's wort has better tolerability than tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs). Of the larger, more rigorous placebo-controlled trials, 2 that required participants to have HDRS scores of ≥20 did not demonstrate a difference between St John's wort and placebo on primary outcomes.[26,27] In the study by Shelton and colleagues,[26] 200 participants with MDD were randomly assigned to St John's wort or placebo for 8 weeks. The primary outcome was decrease in scores on the HDRS; there was not a statistically significant difference between groups. In the trial by the *Hypericum* Depression Trial Study Group,[27] 340 patients with MDD were randomly assigned to St John's wort, sertraline, or placebo. Both St John's wort and sertraline performed similarly to placebo on the primary outcome of change in HDRS scores and response rates as determined by both the HDRS and Clinical Global Impressions rating scales. The *Hypericum* Depression Trial Study Group[27] results specifically raise concerns about placebo-response rates and methodology in many treatment studies of MDD, because sertraline did not perform better than placebo. However, in other large trials, investigators did find a significant difference between St John's wort and placebo in mild to moderate depression (N=375)[28] and a modest, but significant, advantage of St John's wort over fluoxetine (N=135).[29]

St John's wort has significant drug-drug interactions. It induces the metabolism of concomitantly administered medications through the induction of the cytochrome P450 3A4 system, with a possible reduction in therapeutic effects of medications including antiretrovirals, immunosuppressants, antineoplastic agents, anticoagulants, digoxin, oral contraceptives, and hormone replacement therapy.[30,31]

Therefore, St John's wort may be a reasonable treatment for mild to moderate MDD for some individuals, although not all recent studies for the treatment of MDD demonstrated efficacy over placebo. There is greater consensus and support from studies in mild to moderate MDD and less for more severe MDD. Drug interactions limit use and are important safety considerations.

S-adenosyl-L-methionine. S-adenosyl-L-methionine (SAMe) is the major donor of methyl groups in human metabolism. A number of initial small trials demonstrated promise of SAMe given by parenteral administration for MDD.[32] As SAMe is a highly labile compound, several early clinical studies were limited by the rapid decomposition of the SAMe compound administered.[32] However, stable oral preparations of SAMe have been developed, and the administration of SAMe orally was found to be associated with a significant rise of cerebrospinal fluid SAMe, suggesting that oral SAMe is able to cross the blood-brain barrier.[33] In a small open trial, Rosenbaum et al[34] found that non–treatment-resistant patients responded to treatment with oral SAMe. Since the original uncontrolled reports, many double-blind studies have been conducted. In these studies, the parenteral doses of SAMe ranged between 15 and 1,000 mg/d, with most studies using 100 to 200 mg/d; oral doses of SAMe ranged between 400 and 1,600 mg/d, with most studies using 800 to 1,600 mg/d. Overall, SAMe was generally well tolerated in these studies. Side effects included mild insomnia, lack of appetite, constipation, nausea, dry mouth, sweating, dizziness, and nervousness.[35]

Double-blind studies showed that parenteral or oral preparations of SAMe, compared with a number of standard tricyclic antidepressants such as clomipramine, amitriptyline, and imipramine, were generally equally effective and tended to produce fewer side effects.[32] An Agency for Healthcare Research and Quality (AHRQ)[36] meta-analysis of double-blind trials found no significant difference in outcomes between SAMe and conventional antidepressants and superiority of SAMe over placebo. Similarly, in studies examining the efficacy of intravenous or oral SAMe compared with placebo, SAMe was significantly more effective in most studies.[32] The results of the AHRQ meta-analyses are consistent with those of a previous meta-analysis by Bressa.[37]

More recent studies, not included in the meta-analyses, also support the efficacy of SAMe in the treatment of depression. Two studies[38,39] have shown that SAMe, in both its oral and parenteral formulations, was as effective as imipramine. An open trial by Alpert et al[40] showed that half of antidepressant-treated adult outpatients with persisting MDD responded to treatment and nearly half met criteria for remission following antidepressant augmentation with SAMe.

More studies are needed to determine the efficacy of SAMe and its comparative efficacy to standard antidepressants. Promising published studies to date support that more rigorous studies are needed. Definitive studies are still required, as most of the studies thus far are limited by small samples, different delivery methods for SAMe, few comparisons against the newer antidepressants, and even decomposition of early unstable preparations of oral SAMe.

Folate. Folate and several related compounds have received study to ascertain if there is a potential for a role in the treatment of MDD (Figure 1 shows folate and related compounds). Studies to date demonstrate efficacy of augmentation of antidepressants with folic acid (folate), folinic acid (leucovorin), and 5-methyltetrahydrofolate (5-MTHF). These folate forms share an interconversion potential in the complex set of pathways that comprise the 1-carbon cycle.

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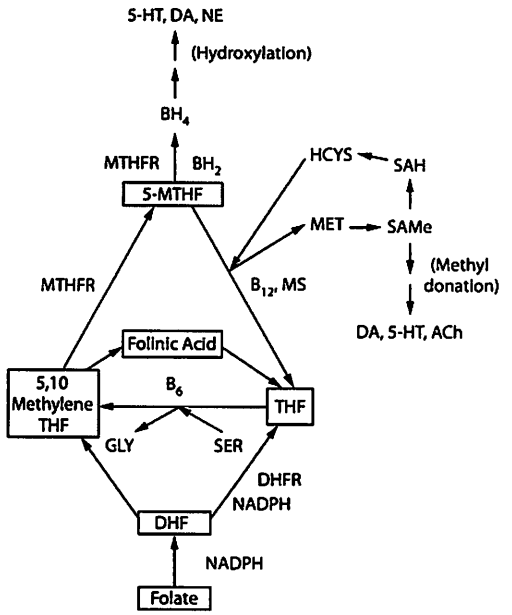
Figure 1. Folate Interconversion Pathways and Neurotransmitter Synthesis



Abbreviations: 5-HT = serotonin (5-hydroxytryptophan), 5-MTHF = methyltetrahydrofolate, ACh = acetyl choline, B_6 = vitamin B_6, B_{12} = vitamin B_{12}, BH_2 = quinonoid dihydrobiopterin, BH_4 = tetrahydrobiopterin, DA = dopamine, DHF = dihydrofolate, DHFR = dihydrofolate reductase, folinic acid = 5-formyl, GLY = glycine, HCYS = homocysteine, MET = methionine, MS = methionine synthase, MTHFR = methylenetetrahydrofolate reductase, NADPH = reduced form of nicotinamide adenine dinucleotide phosphate, NE = norepinephrine, SAH = S-adenosyl homocysteine, SAMe = S-adenosyl-L-methionine, SER = serine, THF = tetrahydrofolate.

These reactions, which in turn depend on B_{12} and homocysteine availability, are postulated to exert an antidepressant effect by impacting the synthesis of neurotransmitters such as norepinephrine, dopamine, and serotonin.

The efficacy of folate monotherapy for MDD has yet to be adequately tested. A few trials have found folate to be efficacious and well tolerated, although the best dose and form of folate remain unclear. Coppen and Bailey[41] conducted a randomized trial in which patients with MDD were given fluoxetine plus either folic acid or placebo. Patients who received adjunctive folic acid experienced a greater response to fluoxetine and reported fewer adverse events. However, when men and women were analyzed separately, only women had substantial improvement with folic acid augmentation. Furthermore, since certain polymorphisms that impair methylation processes and the conversion of folate into its active form, methylfolate, have been found to be overrepresented in individuals with depression, methylfolate may be a more effective form of folate supplementation because it is able to penetrate the blood-brain barrier.[42]

Several open and blinded studies of methylfolate monotherapy in a variety of depressed populations have found that patients experienced significant improvement in depressive symptoms with no drug-related adverse events. Populations that have been examined include elderly patients with MDD[43] and patients with comorbid alcoholism and MDD.[44] A sample of patients with dementia and depressive symptoms as quantified by the HDRS experienced significant improvement in depressive symptoms and immediate recall compared to a group that received low-dose trazodone.[45] Another randomized study[46] using methylfolate as adjunctive therapy for folate-deficient patients with MDD or schizophrenia found that patients experienced a greater reduction of symptoms compared with patients receiving placebo augmentation. Although placebo-controlled data are needed, initial studies indicate that methylfolate may be a safe and effective option for the treatment of depression, especially in populations that are vulnerable to medication-related adverse events and those who are folate deficient.

Other researchers have used leucovorin, a form of folinic acid that is converted into methylfolate. Alpert and colleagues[47] used leucovorin to augment treatment for MDD in patients who were not folate deficient. The participants had experienced partial response or nonresponse to antidepressant treatment. The investigators found a significant reduction in depressive symptoms in the folate group, although only 19% reached remission. In another study of patients with MDD, bipolar depression, and schizoaffective disorder, investigators found that folate augmentation enhanced lithium response in patients treated for bipolar and unipolar depression, particularly among those with low folate levels.[48]

Evidence to date suggests that folate and methylfolate monotherapy may offer benefits for subpopulations with depression, but more studies are needed, especially to assess efficacy as monotherapy. Additional studies to determine which forms of folate cross the blood-brain barrier to affect brain levels and to determine efficacious doses are needed. Additional investigation is therefore needed to better characterize those who may be most responsive to folate augmentation.

Folate augmentation of antidepressants appears to be a low-risk and reasonable part of a treatment plan for individuals with MDD, and more research is needed to fully elucidate the role of folate and related compounds in the treatment of MDD.

Bright light therapy. Since the original report of light treatment for seasonal depression,[49] a large evidence base supporting its efficacy has evolved. In 1998, 3 of the largest light therapy studies for seasonal affective disorder were published together and demonstrated the efficacy of morning light therapy compared with nonlight placebo controls[50,51] and evening light administration.[51,52] An American Psychiatric Association study group published a meta-analysis of light therapy for depression.[53] Based on 8 studies with stringent inclusion criteria, a significant, large effect size was demonstrated for seasonal affective disorder (0.84; 95% CI, 0.60–1.08; $P<.0001$). This report indicated that the therapeutic effect of light was at least equivalent to and potentially greater than that of antidepressants. Lam et al[54] compared light therapy to fluoxetine for the treatment of seasonal affective disorder. Patients (N = 98) were randomly assigned to 8 weeks of treatment with morning light (30 minutes)

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of 10,000 lux plus a placebo capsule, or dim morning light (100 lux = placebo) plus 20 mg of fluoxetine. Both treatment groups improved similarly, with no significant differences in response rates (67% for each group) or remission rates (50% for light; 54% for fluoxetine). Post hoc analysis revealed that the response to light therapy observed after 1 week of treatment was earlier than that associated with fluoxetine. Although both treatments were well tolerated, the rate of adverse events was lower with light compared to fluoxetine.

In contrast, the efficacy of light therapy as a treatment for nonseasonal depression is less well established. Positive publications include meta-analyses by Tuunainen et al,[55] who reported a modest antidepressant effect, and by Golden et al,[53] who found an effect size of 0.53 (95% CI, 0.18–0.89; $P < .003$), based on 3 studies. In a third meta-analysis, Even et al[56] concluded that bright light exposure was not convincingly efficacious as a monotherapy for nonseasonal depression, with 3 positive and 4 negative studies that met strict inclusion criteria. In one study,[57] patients with chronic depression were randomly assigned to bright light (10,000 lux; n = 10), high-density ions (n = 12), or low-density ions (n = 10; placebo control). Remission rates were 50% for bright light, 50% for high-density ions, and 0% for low-density ions. Finally, 2 small pilot studies[58,59] in pregnant women with nonseasonal depression demonstrated promising results.

Light therapy has demonstrated a more convincing benefit as an adjunctive treatment to antidepressant drugs rather than a monotherapy for nonseasonal depression. In their meta-analysis, Even et al[56] observed that 4 of 5 studies supported the efficacy of light therapy with antidepressant drugs. The largest RCT to date included 102 patients treated with sertraline (50 mg/d).[60] The subjects also received randomized augmentation treatment with 30 minutes of either bright morning (10,000 lux) or dim red (50 lux) light for 5 weeks. All clinician- and self-report measures significantly favored active light augmentation.

The mechanism by which light therapy exerts an antidepressant effect is not known. The most prominent hypothesis is a "phase shift" model, which proposes that seasonal affective disorder is associated with a delay in the timing of circadian rhythms relative to the timing of sleep, which is corrected by properly timed early morning light therapy.[52]

The dosing of light therapy has been elucidated in 4 dimensions: intensity, exposure duration, spectrum, and time of day of administration.[61] The preferred light therapy apparatus is a commercially produced fluorescent box with a light intensity of 10,000 lux. Broad spectrum white illumination is recommended with attenuation of wavelengths < 450 nm (which includes far-blue and ultraviolet) and infrared radiation, both of which present ocular risks.[61] The effective broadband white spectrum can vary in color across the range including 3,000 Kelvin (K) (soft white), 4,000 K (cool white), 5,500–7,000 K (daylight, or "full spectrum"), and 17,000 K ("blue enhanced").[61] To utilize light therapy, patients sit in front of a downward tilted light box that is situated 12 to 14 inches from their eyes. They can engage in other activities compatible with maintaining their position in front of the box. The standard starting dose of light is 10,000 lux for 30 minutes in the morning.

The most common side effects of bright light exposure are nausea, jitteriness, and headache.[62] Side effects are usually mild and relieved with a decrease in the light dose. Ophthalmology consultation is appropriate when bright light therapy is administered with photosensitizing drugs. For instance, examples of medications that may be photosensitizing include some antibiotics, nonsteroidal anti-inflammatory drugs, diuretics, St John's wort, and statins. Patients with bipolar depression are vulnerable to mania induction or mixed state development.[63]

In summary, light therapy is an evidence-based, effective, well-tolerated treatment for seasonal affective disorder, as well as an augmentation strategy for antidepressant treatment of nonseasonal depression. Light therapy is inexpensive and amenable to rapid dose changes based on the effects observed from the previous day and can be delivered in patients' homes. Study sizes have generally been small. Colored or white dim light and inactive negative air ionizers have served as placebo controls. Light intensity and duration manipulations suggest a dose-response function, and circadian timing variations have shown reliable differential group effects with morning light superiority.

Bright light therapy may be a reasonable treatment for MDD, best studied as a monotherapy and less studied as an augmentation strategy, with particularly well-established benefit in seasonal MDD.

Acupuncture. The evaluation of the efficacy of acupuncture in the treatment of MDD poses many challenges. These include concurrent use of other treatments, conceptual differences between Chinese and Western medical diagnoses, and the use of disparate acupuncture protocols across studies. Four systematic reviews on acupuncture for depressed mood have recently been published in English-language journals.[64–67] Three of these included only English-language manuscripts.[64–66] Systematic reviews and meta-analyses have yielded inconsistent conclusions regarding efficacy, and there is a lack of adequate studies comparing manual acupuncture and/or electroacupuncture to control conditions. Participants in treatment studies generally experienced improvement with both active and sham acupuncture. The recent systematic review conducted by Wang et al[67] included Chinese-language publications. Of 200 trials of acupuncture for the treatment of depression, 8 small sham acupuncture controlled studies (total N = 477) included in the meta-analysis compared manual acupuncture, electroacupuncture, or laser acupuncture with sham acupuncture only. The authors found evidence of beneficial effects of acupuncture in improving the clinical global impression score of depressed patients, but heterogeneity of study designs and small sample sizes precluded conclusions about response and remission rates.[67]

Studies differ by type of acupuncture, duration of sessions, frequency of sessions, and total number of sessions. These factors may introduce confounding variables that limit analysis of pooled treatment outcomes from heterogeneous

study designs. In addition, studies have other serious methodological flaws, including small sample sizes, inconsistent randomization and blinding, often brief duration, and lack of follow-up.[66]

Acupuncture is generally low risk. Uncommon transient adverse effects associated with acupuncture include bruising, fatigue, and nausea. Serious complications related to acupuncture are extremely rare and include infection with human immunodeficiency virus and hepatitis B and C due to use of nonsterilized needles.[68] Adverse events may vary depending on the skill of the practitioner, and serious adverse events are uncommon.

Critiques of the systematic reviews of acupuncture have raised questions regarding methodology, assessment, and interpretation of the literature.[69,70] For example, Halbreich[70] recently assessed systematic reviews of acupuncture and highlighted concerns about disparities between reviews, including partial overlap between separately published studies.

Two studies have assessed acupuncture augmentation of antidepressant medications.[71,72] Some studies of acupuncture for MDD have included specific populations, such as pregnant women.[73,74] Of note, Manber and colleagues[75] recently published a rigorous RCT of acupuncture for the treatment of MDD in 150 pregnant women with verified diagnoses of MDD. They received 8 weeks of treatment, consisting of 12 treatments in one of 3 groups: (1) acupuncture specific to depression, (2) control acupuncture that was not specific to the treatment of depression, or (3) massage. A greater rate of decrease on the HDRS and greater response rate (63%) were found with depression-specific acupuncture compared to control acupuncture and massage (37.5% and 50% response rates, respectively).

When the above studies are excluded on the basis of methodological flaws or specialty study populations, only 2 well-designed sham-controlled studies remain, both conducted by the same research group.[69,74] One of these was a small study (N = 33) that found efficacy of individualized acupoints addressing unique clusters of depressive symptoms in moderately depressed women.[69] However, a subsequent study in a larger heterogeneous population (N = 151) that included men and women with MDD failed to replicate the beneficial effects of acupuncture compared to a sham-acupuncture placebo.[75]

In an assessment of studies using acupuncture published during the period 1996–2005, Derry et al[76] concluded that it is premature to state that acupuncture is efficacious for any indication, mainly because study sample sizes in RCTs have been inadequate to draw meaningful results. Since that review, 2 Cochrane reviews have supported the use of acupuncture in headaches.[77,78]

In sum, evidence for the efficacy of acupuncture as a primary treatment of depression is inconclusive, and studies to date have failed to demonstrate efficacy of acupuncture compared to a control condition for the treatment of MDD. Large controlled trials with improved randomization, double-blinding, and agreement on a uniform sham protocol, as well as analysis of different "active" acupuncture protocols, means for taking into account differences in training and experience of persons administering treatment, and uniform statistical methods for measuring outcomes, are needed. Consensus on criteria for designing clinical trials, selecting and ranking "well-designed" studies, and reporting future trials in the peer-reviewed English-language journal literature is necessary to achieve these goals.

At this time, most of the data do not suggest that acupuncture is an efficacious treatment for MDD. Although overall risks may be low, rigorous trials to date that support efficacy are lacking.

Exercise. Findings from community-based cohort studies support an association of exercise with a reduction of depressive symptoms and improved mental health. Galper et al[79] examined data from 5,451 men and 1,277 women enrolled in a cohort study evaluating morbidity and mortality rates associated with physical activity and fitness. Depressive symptoms and well-being were assessed with the Center for Epidemiologic Studies Depression Scale and the General Well-Being Schedule, respectively. Participants also underwent a maximal treadmill test and completed a comprehensive questionnaire to assess participation in physical activities. Male and female participants with higher levels of physical activity and physical fitness reported fewer depressive symptoms and greater well-being compared with those with lower levels. The Black Women's Health study reported similar findings from an ongoing research study investigating risk factors for major illnesses in adult African American women.[80] Vigorous physical activity was associated with a reduced odds ratio for depressive symptoms.

Exercise has been examined as a treatment for depression, both as monotherapy and as augmentation to antidepressants. Results from 2 meta-analyses of exercise for depression have recently been published,[81,82] one of which specifically involved elderly subjects.[82] Despite methodological variability, investigations have generally shown exercise to have positive effects on mood in both men and women across a wide age range, irrespective of the setting (eg, inpatient or home-based exercise) or mode (eg, aerobic or weight-training). Furthermore, patients who continued to exercise following study participation had a lower risk of relapse over several months to years.

The Depression Outcomes Study of Exercise (DOSE) was one of the first RCTs to examine the efficacy of exercise as a monotherapy for mild to moderate MDD.[83] The investigators used a 2 × 2 factorial design with a flexibility exercise "placebo" control to examine the effect of different "doses" of exercise in men and women aged 20–45 years. The 2 manipulated exercise factors were total energy expenditure and exercise frequency (days per week). High energy expenditure was 180–210 minutes of exercise per week (consistent with public health recommendations), and participants in this group were referred to as the public health dose (PHD) cohort. Low energy expenditure was approximately 80 minutes of exercise per week, and these participants comprised the low-dose (LD) group. The 2 frequencies were 3 and 5

days per week. Participants were randomly assigned to one of 5 groups that included PHD over 3 days per week, PHD over 5 days per week, LD over 3 days per week, LD over 5 days per week, or a stretching control group (15 minutes on 3 days per week). For all conditions, the first 12 weeks of exercise was conducted under supervision, and then 12 weeks of exercise was performed at home or at another facility. HDRS was administered weekly and served as the main outcome measure.

The PHD group showed a 47% reduction in symptoms at 12 weeks compared with reductions of approximately 30% each for the LD and control groups. The difference in remission rates between the PHD group and the control group was significant ($P = .01$). Neither age nor gender had a significant effect on treatment outcomes. Exercise frequency also had no impact on mood improvement, which suggested that the amount rather than the frequency of exercise is critical to response.

More recently, Blumenthal and colleagues[84] reported results from a study of adult men and women with MDD. Participants were randomly assigned to one of 4 conditions for 16 weeks: supervised group exercise, home-based exercise, double-blind sertraline (50–200 mg/d), or placebo pill. The primary outcome measure was the rate of remission (defined as an HDRS score of < 8). Participants randomly assigned to active treatments had nonsignificantly higher remission rates than those receiving placebo. Similarly, there were no significant differences in HDRS scores among the groups after treatment. These data suggest that the efficacy of exercise may be similar to that of sertraline, although larger, definitive studies are needed.

The majority of studies examining exercise as a treatment for depression have investigated exercise as an adjunct to antidepressants. Blumenthal et al[85] compared the effects of group exercise, medication, and group exercise in combination with medication in older adults (aged 50–77 years) with mild to moderate MDD over a 16-week, acute-phase RCT. Group exercise alone was as efficacious as both medication and combined treatment in reducing symptoms of depression. The extension of that study examined the continued efficacy of exercise by conducting a 10-month follow-up from the earlier acute-phase study.[86] Patients in the group exercise–alone group had a significantly increased likelihood of remission ($P = .01$) compared with the medication-alone group, and there was a reduced likelihood of relapse in the exercise-alone group (30%) compared with both the medication-alone group (52%) and the combined group (55%). Furthermore, regular aerobic activity was associated with a decreased likelihood of being classified as depressed at follow-up. However, the naturalistic design of the follow-up study made interpretation of results complicated, since many participants changed their treatment regimen following the acute phase. Although the analyses did not account for changes in regimen, this study does provide additional support for the use of exercise in the treatment of depression and suggests that the beneficial effects may be long-lasting.

Martinsen et al[87] assessed 43 patients hospitalized for depression who were receiving individual psychotherapy and occupational therapy, 24 of whom were randomly assigned to aerobic exercise with existing treatment and 19 of whom comprised the control group (no exercise added). Although use of tricyclic antidepressants was not controlled for in the analyses, 14/19 in the control group and 9/24 in the exercise group were taking these medications during study participation. The authors reported a significantly larger difference ($P < .05$) in Beck Depression Inventory (BDI) scores between baseline and 9 weeks in the exercise group compared to controls. Similarly, Veale et al[88] investigated whether the addition of aerobic exercise would enhance participants' standard treatments for depression in 2 related, randomized studies involving 124 participants. In the first, subjects either continued their usual treatment (control group) or added 3 supervised aerobic group exercise sessions per week for 12 weeks. Depressive symptomatology was assessed using the Clinical Interview Schedule (CIS) and the BDI. Mean CIS scores at week 12 were significantly lower in the exercise group compared to the control group ($P < .005$), although reductions in scores were observed for both groups. BDI scores were also reduced in both groups, but no significant differences were found; however, it should be noted that higher baseline scores were present in the control group ($P < .05$). In the second study, a low-intensity exercise regimen consisting of stretching and yoga was compared with the aerobic protocol used in the first study. Both types of exercise produced nonsignificant reductions in CIS and BDI scores at week 12. Dimeo and colleagues[89] conducted a pilot study in which 12 medication-treated individuals diagnosed with MDD or bipolar I disorder completed a short-term exercise intervention (30 minutes per day for 10 days). Significant differences were found on the HDRS and the Scale for Self-Assessment of Depression between day 1 and day 10 on both measures.

Additional studies have examined the effect of the addition of exercise for patients with a partial response to antidepressants. In one study[90] aimed at the assessment of exercise adjunctive to antidepressants in older individuals, participants were eligible if they had been treated with antidepressant medication for ≥ 6 weeks without a sustained response (defined by a Geriatric Depression Scale score of ≥ 10). Eighty-six participants were randomly assigned to attend group exercise classes consisting of weight-bearing exercise, or health education classes (nonexercise control group) twice weekly for 10 weeks. In both groups, sessions lasted for approximately 45 minutes. After 10 weeks, 55% (23/42) of the exercise group achieved an $HDRS_{17}$ score reduction of ≥ 30%, whereas only 33% (14/43) of the control group achieved such a reduction. Trivedi et al[91] conducted an open-label pilot study in depressed individuals (aged 20–45 years) with MDD. To be eligible, participants had been treated with an antidepressant for ≥ 6 weeks with partial benefit, but were still experiencing residual symptoms, as indicated by an HDRS score of ≥ 14 at entry. Eligible participants began a 12-week adjunctive intervention of aerobic

exercise, administered in a combined supervised and home-based protocol, while antidepressants were continued at the same dose as prior to study entry. In general, participants reported a moderate level of depression severity at baseline. A beneficial effect of the addition of exercise was demonstrated by a mean reduction of 5.8 points in HDRS scores in the intent-to-treat analysis. Improvements in quality of life were also reported. This pilot trial led to the development of the Treatment with Exercise Augmentation for Depression (TREAD) study,[92] an ongoing randomized controlled trial examining SSRI augmentation using a public health recommended dose of exercise or a low dose of exercise. The investigation was specifically designed to address some of the major existing limitations of exercise studies to date; namely, the use of group exercise, blinded evaluation of outcome measures, and rigorous diagnostic evaluation.[92]

Studies have consistently demonstrated a reduction in depressive symptoms as a result of exercise treatment. However, many trials examining augmentation of drug therapies with exercise have not adequately controlled for the type, duration, or response to the initial treatment. Methodological issues that should be taken into account include adherence to exercise or control conditions, nonexercise factors that may be associated with a group exercise regimen (such as social contact), and quality of blinding. The symptoms of depression may also impact motivation to participate in exercise programs. It is possible that individuals who choose to enter exercise trials may have certain characteristics that differ from those of the general depressed population, and these may impact the generalizability of the findings.

In summary, preliminary data support the addition of exercise to treatment regimens for patients with MDD. Exercise confers multiple health benefits, and advocating for its integration into routine MDD treatment is medically appropriate.

CAM Psychotherapies

We have identified 3 alternative forms of psychotherapies that are not currently considered conventional practice but that have an accumulating evidence base from randomized clinical trials in MDD: (1) mindfulness-based cognitive therapy, (2) problem-solving therapy, and (3) well-being therapy.

Mindfulness-based cognitive therapy. Mindfulness-based cognitive therapy (MBCT) has been developed with the goal of preventing relapses and recurrences of major depressive disorders.[93] MBCT combines mindfulness training[94] with elements of cognitive-behavioral therapy for depression.[95] Patients learn to recognize and disengage from negative and ruminative thinking.[93] In a recent systematic review by Coelho and colleagues,[96] 4 studies were identified comparing MBCT plus treatment as usual (TAU) with TAU alone, including 2 RCTs, 1 study based on a subset of one of these trials, and 1 nonrandomized trial. For patients with 3 or more previous episodes of MDD, the RCTs reported lower relapse hazard rates for MBCT-plus-TAU patients compared with the TAU-only patients. For patients with 2 previous MDD episodes, no significant differences between groups were found in the hazard of relapse or recurrence over the study period.

In a recent open study of MBCT augmentation of psychotherapy and medication treatment for currently depressed patients with treatment-resistant depression,[97] a significant decrease in depression and anxiety levels was found for individuals who received MBCT (using an intent-to-treat analysis).

Problem-solving therapy. Problem-solving therapy has been examined in several RCTs. There are different types of problem-solving therapy for depressive disorders, including social problem-solving therapy, problem-solving therapy for primary care, and self-examination therapy. Results of 13 randomized trials of problem-solving therapy have been integrated in a comprehensive meta-analysis conducted by Cuijpers et al.[98] Most studies found favorable results for problem-solving therapy for the treatment of MDD. However, heterogeneity was very high in almost all analyses, and the effects varied enormously between studies. The overall effect indicated moderate to large effects of problem-solving therapy on depressive symptoms, depending on the model of analyses ($d=0.34$ in the fixed effects model and $d=0.83$ in the random effects model), format (group interventions had larger effects than individual interventions), diagnosis (studies including only subjects with MDD had smaller effect sizes), type of problem-solving therapy (social problem-solving therapy having the largest and problem-solving therapy for primary care having the smallest), type of analysis (intent-to-treat analyses resulted in smaller effect sizes), and type of control group (studies with waiting-list control groups had the largest effect sizes). A stronger evidence base is required, and the effectiveness of problem-solving therapy in routine practice must be evaluated.

Well-being therapy. Well-being therapy is a specific psychotherapeutic strategy for enhancing well-being, based on Ryff's[99] multidimensional model of psychological well-being and encompassing 6 dimensions: autonomy, personal growth, environmental mastery, purpose in life, positive relations, and self-acceptance.[99,100] The goal of this short-term therapy is to improve patients' levels of psychological well-being through cognitive-behavioral techniques.[97] Well-being therapy is structured, directive, problem-oriented, and based on an educational model. Well-being therapy was originally designed as a specific psychotherapeutic strategy for residual symptoms of affective disorders.

In the past decade, several investigations have suggested the usefulness of well-being therapy as a sequential method of treatment, based on the use of pharmacotherapy in the acute phase of depression and well-being therapy in its residual phase. This approach was applied to 40 patients with recurrent MDD who had been successfully treated with antidepressants that were tapered and discontinued. Patients were randomly assigned to either well-being therapy with CBT or clinical management. At a 2-year follow up, well-being therapy plus CBT treatment resulted in a significantly lower relapse rate (25%) than did clinical management (80%).[101]

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Table 1. Selected CAM Treatments in MDD: Clinical Considerations

Treatment	Efficacy as Monotherapy	Efficacy as Adjunctive Treatment	Safety	General Health Considerations	Cost, Accessibility, Other Considerations
St John's wort	Efficacy supported by placebo-controlled trials and equivalence trials with antidepressants; conflicting results with severe MDD, best established with mild to moderate severity of symptoms	Not available	Relatively low risk of side effects[a]; risk of drug interactions	No established added benefit over antidepressant effects	Accessible without a prescription; generally low cost
SAMe	Efficacy supported by placebo-controlled trials and equivalence trials with antidepressants	Limited study as an augmentation treatment	Relatively low risk of side effects[a]	Possible benefits for arthritis, liver disease (AHRQ review)	Expensive; accessible
Omega-3 fatty acids	Limited and conflicting results as a monotherapy	Preponderance of studies demonstrate benefit as augmentation	Low risk of side effects	Well-established health benefits, recommended by American Heart Association	Accessible; low cost
Exercise	Limited evidence for use as monotherapy	Limited evidence for use as augmentation strategy	Few medical contraindications	Well-established health benefits	Accessible; low cost
Light therapy	Placebo-controlled trials demonstrate benefit as monotherapy	Limited study as augmentation strategy	Low risk of side effects[a]	No known additional health benefits	Cost of light box; unclear efficacy of natural sunlight vs light box
Acupuncture	Conflicting findings in controlled studies; meta-analyses do not demonstrate positive effects	Insufficient study as augmentation treatment	Low risk of side effects	No known added benefit for depression-specific acupuncture, although acupuncture is practiced for other indications in Eastern medicine	Need skilled provider; may or may not be covered by insurance
Folate	No evidence for efficacy as monotherapy	Appears to have efficacy in limited study as augmentation treatment (especially in women)	Can mask pernicious anemia	Prophylaxis of neural tube defects in women of reproductive age	Accessible, inexpensive
Psychotherapies	Limited evidence as monotherapy	Insufficient study as augmentation	Low risk of side effects	Overall stress reduction	Requires skilled provider

[a]Case reports of mania with St John's wort, SAMe, and bright light therapy.
Abbreviations: AHRQ = Agency for Healthcare Research and Quality, CAM = complementary and alternative medicine, MDD = major depressive disorder, SAMe = S-adenosyl-L-methionine.

The differential relapse rate was significantly related to the resolution of residual symptoms.[102] At 6-year follow-up, this well-being therapy plus CBT treatment continued to result in a significantly lower relapse rate (40%) than did clinical management (90%).[103] However, these positive results from studies of well-being therapy need to be confirmed with large-scale controlled studies.

The limitations of these psychotherapies must be considered. In terms of accessibility to CAM psychotherapies, not all patients will have access to skilled providers. Consistent with other psychotherapies, these treatments may be cost-prohibitive for some patients and less appealing than pharmacologic interventions because of the significant time commitment required. Particular psychotherapeutic approaches may be most effective for patients who are motivated to pursue the work involved in the specific therapy and are able to attend a sufficient number of treatment sessions.

At this time, these psychotherapies appear promising and deserve further study. Most psychotherapies are considered low-risk, but it would be prudent for future studies to include assessments of tolerability and patient adherence to regimens.

DISCUSSION

The therapies reviewed in this report were included because they have received scientific study for the treatment of MDD and, in the opinion of this task force, deserve more rigorous study to determine their place in the therapeutic armamentarium. Our focus on treatments for MDD was based on the prevalence of MDD, the popularity of CAM treatments for MDD, the relatively large number of RCTs for MDD, and the public health significance of the CAM-MDD interface. Clinical and research considerations regarding these treatments are summarized in Tables 1 and 2.

A review of RCTs for commonly used CAM treatments suggests that more rigorous and larger studies are essential to determine whether any of these treatments should be formally indicated for the treatment of MDD. Studies support the use of SAMe in MDD as a monotherapy, although more rigorous studies are needed, as those published are limited by small sample sizes and different methods of administration of SAMe, with some inconsistencies noted across preparations. Regarding St John's wort, which has primarily been studied as a monotherapy, there is greater consensus for use in mild to moderate MDD and less for use in more severe

Table 2. Research Issues Related to CAM Treatments in MDD

Modality	Areas Needing More Research	Challenges in Research Methodology
St John's wort	Use in MDD prevention; what drug interactions are clinically significant? (pharmacokinetic studies?)	Difficulties in performing combination and augmentation studies in view of risk of interactions
SAMe	Comparison of efficacy to standard antidepressants and as augmentation (large trials underway); prevention of recurrent MDD; use in chronic depression and TRD; use in special populations	Consolidation/comparison of findings and doses from studies using different delivery systems for SAMe, ie, oral, intramuscular, and intravenous
Omega-3 fatty acids	Formulation: EPA vs EPA + DHA; dose; fish intake vs capsules; prevention studies of primary disease and recurrent MDD; monotherapy requires more study	Concerns over confounding effects of unreported smoking; controlling for impact of omega-3 obtained in the diet
Exercise	Prevention of recurrent MDD (there are prevention data in epidemiologic studies, also specifically for some medical conditions); type/dose of exercise; recommendations for special populations—children, gender, etc	Blinding of trials, selection of placebo; Social effects of group exercise programs; characterization of personality factors in patients who are drawn to participate in exercise studies and impact on generalizability of findings
Light therapy	Maintenance treatment, TRD; natural sunlight vs light box therapy in nonseasonal MDD; additive effects of light + exercise	Difficulty in performing comparison trials with standard agents, in view of need for different placebos
Acupuncture	Conflicting data for acute MDD; prevention; chronic MDD; prevention of relapse	Blinding of trials, selection of placebo; difficulty in performing comparison trials with standard agents, in view of need for different placebos
Folate	Role for folate levels in routine MDD treatment? Larger adjunctive studies; mechanistic studies examining activity of different folate forms	Impact of routine folate fortification in diet on effect sizes observed in supplementation studies
Psychotherapies	Large, controlled trials to determine efficacy and feasibility	Blinding of trials, selection of control conditions

Abbreviations: CAM = complementary and alternative medicine, DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, MDD = major depressive disorder, SAMe = S-adenosyl-L-methionine, TRD = treatment-resistant depression.

MDD. Drug interactions limit use and are important safety considerations. Research supports the use of omega-3 fatty acids as a low-risk adjunctive treatment in MDD. While it is premature to recommend folate augmentation and exercise on the basis of efficacy in randomized controlled treatment trials for MDD, established health benefits and low risk may make these attractive components of treatment plans. At this time, data do not suggest consistently that acupuncture is an efficacious treatment for MDD, although a small number of findings suggest further research is warranted; most recently, an RCT demonstrated a benefit for MDD in pregnant women.[75] Although overall risks of acupuncture may be low, rigorous trials to date are lacking that support efficacy. At this time, CAM psychotherapies appear promising and deserve further study. Most psychotherapies are considered low-risk, but it would be prudent for future studies to include assessments of tolerability and adherence.

Available treatments for MDD often fall short in terms of efficacy and tolerability. Safe, effective, and accessible treatments are still needed for MDD and other psychiatric disorders. Patients often perceive CAM modalities as less stigmatizing and more attractive than conventional treatments. Some health care providers also find CAM treatments attractive because they are labeled as "CAM" or "natural." We urge balanced consideration for CAM therapies and caution against overenthusiasm—or underenthusiasm—for categorization as CAM. Individual treatments need to be weighed on the basis of scientific evidence regarding efficacy and safety. Safety must also be a focus of further study of CAM therapies, and, of note, adverse events may not be systematically reported as they are with FDA-approved medications.

Efficacious CAM therapies could importantly expand the "toolbox" of evidence-based therapies and engage more patients in treatment. Patient preference is an important and poorly understood topic in psychiatric treatment research. Participants in trials of CAM treatments may differ in comparison to those who participate in standard antidepressant trials.

The greatest risk of pursuing one of these therapies or other understudied treatments is the possible delay of other efficacious treatment in the case of inadequate response. Severity of the major depressive episode, suicidality, and other safety issues must be evaluated for appropriateness prior to trials of novel interventions. An additional consideration is cost, as many of the treatments discussed in this report are not routinely covered by health insurance.

Many CAM treatments are easily accessible and available without a prescription. Some individuals may find it easier to forgo standard diagnosis and the opportunity to be presented with all treatment options. Our Task Force recommends that all individuals with psychiatric symptoms and diagnoses receive a full evaluation from a psychiatrist or other qualified mental health care professional and be monitored for assessment of efficacy, side effects, and symptomatic worsening. Some of the CAM treatments reviewed in this report have been studied as monotherapy, while others are most established as adjunctive treatments to standard therapies. Therefore, the evidence and role for each therapy must be understood by health care providers and patients in order to utilize CAM therapies appropriately.

Psychiatrists and other physicians must be prepared to discuss CAM therapies with patients and balance the benefits and risks with those of conventional therapies. Eliciting patient histories of CAM use and appropriate incorporation of CAM use in treatment planning must be formal parts of training and education.

More research regarding CAM treatments in psychiatry is imperative. Studies must have appropriate control conditions

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and adequate power to yield definitive data. Funding for studies is challenging, as industry support is not often available for some treatments that could have great public health significance. In addition to further rigorous, well-powered studies of individual CAM treatments, we encourage studies of the comparative effectiveness of CAM compared to that of standard treatments.

Drug names: clomipramine (Anafranil and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), leucovorin (Fusilev), lithium (Lithobid and others), sertraline (Zoloft and others), warfarin (Coumadin).

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