

Complementary and Alternative Medicine in Major Depressive Disorder: The American Psychiatric Association Task Force Assessment of the Evidence, Challenges, and Recommendations

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Prepared by Task Force on Complementary and Alternative Medicine

INTRODUCTION

Complementary and Alternative Medicine (CAM): Definitions and Prevalence of Use in Psychiatric Disorders

Complementary and Alternative Medicine (CAM) is a term used to represent a number of specific treatments with potentially high public health importance and benefits. That which constitutes conventional or mainstream medicine is subjective and evolves over time. "Complementary" refers to approaches that are not considered mainstream or conventional, but are consistent with Western concepts based on the biomedical model. "Alternative" approaches are usually considered outside of the traditional Western medical conceptual framework. "Integrative" medicine refers to the combination of CAM and conventional treatments with the goal of achieving the best clinical outcomes for patients. CAM has also 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" (NCCAM, 2002).

Many CAM treatments are commonly used and readily accessible, though few have received adequate study for psychiatric conditions. CAM use has increased in recent decades (Eisenberg et al., 1998; Barnes et al., 2008). It is not well established how often CAM treatments are prescribed by a health care provider, in comparison to self-prescribed. Approximately 72 million adults in the U.S. use at least one CAM therapy annually, representing over one-third of the population (Tindle et al., 2005). Many individuals with psychiatric disorders turn to CAM either as adjunctive to or in lieu of conventional therapies. In a survey of CAM utilization, one research group reported that approximately 10% of U.S. adults surveyed who had visited a CAM provider had a self-reported psychiatric diagnosis, and approximately half of those respondents had sought care from a CAM provider specifically for a psychiatric indication (Druss and Rosenheck, 2000). Simon et al. (2004) assessed visits to CAM providers, and found 11% of visits were sought for mental health conditions in a representative sample of naturopathic physicians, acupuncturists, chiropractors, and massage therapists. The majority of patients were self-referred and care with conventional medical providers was poorly coordinated. In a survey of a nationally representative U.S. sample, Kessler et al. (2001) found that over half of respondents with self-reported depression or anxiety disorders used CAM therapies, although only a small proportion were doing so in coordination with a conventional health care provider. 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 (Elkins et al., 2005). Major depressive disorder (MDD) was the most common diagnosis associated with CAM use. Of importance, most of these patients had not

disclosed CAM use to their psychiatrist (79%). Unutzer et al. (2000) 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 particular association of CAM use for highly prevalent mental illnesses, compel psychiatrists to understand the benefits and risks of CAM, as well as the role of CAM treatments in health care.

Methodology and Limitations: Evaluation of Evidence in MDD and Application to CAM

The practice of evidence-based treatment in psychiatry is frequently limited by inadequate data on the efficacy and safety of treatments, methodological limitations of research studies, and the inherent limitations of our diagnostic and assessment procedures. These general challenges apply to the study of all treatments that are used for MDD, whether conventional or nonconventional, and are not specific to CAM treatments. Psychiatric diagnoses lack simple diagnostic tests, depending instead upon diagnostic criteria arrived at by consensus. The classification of disorders and nomenclature change over time, as evidenced by iterative versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM) classification, published by the American Psychiatric Association. The gold standard of diagnosis used in research is a validated structured interview that adheres to current DSM diagnostic criteria. Failure to determine diagnostic criteria at study entry to validate a diagnosis compromises interpretation of study results. Additionally, response and remission must be adequately reported with validated measures to provide consistency in intervention research for a particular disorder.

Placebo control groups are often considered the gold standard control for randomized controlled trials (RCTs) of medications. Other control conditions are often utilized, such as active (e.g., an established therapeutic agent) and non-active (e.g., waitlist) control groups.

The high rate of placebo response in MDD treatment studies makes uncontrolled trials difficult to interpret (Fava M et al, 2003a). Even in placebo-controlled trials for MDD, the magnitude of the placebo response poses challenges to the study of antidepressant treatments (Walsh et al., 2002; Stolk et al., 2003). Many studies of treatments for MDD lack statistical power to demonstrate a difference between active treatment and placebo, yet the conduct of larger, more resource-intensive studies is usually dependent upon positive pilot data. Novel treatments may not receive adequate exploration when small pilot trials fail to demonstrate statistically significant results. High placebo response rates complicate interpretation of studies, even in the case of established, U.S. FDA-approved antidepressant medications (Kirsch et al., 2008). Additionally, placebo control conditions pose ethical considerations, because MDD is a serious disorder with significant morbidity and mortality. Adequate trials of some treatments may require longer studies, and longer placebo-only arms of studies increase concerns about lack of established treatment for participants.

Generalizability is also a concern in antidepressant treatment studies. Historically, individuals with certain comorbid psychiatric and medical conditions have been excluded from MDD treatment studies. Due to the high rates of comorbidity among individuals with MDD, this practice severely limits the generalizability of findings to individuals in routine clinical practice (Zimmerman et al., 1994; Fava et al., 2003b). Also, it is unclear whether individuals who are willing to enter RCTs are representative of people with MDD as a whole.

The accessibility of many CAM treatments may add to the methodological challenges of their study. Some patients may infer that modalities under study are effective, and may seek their use outside of protocols. This was documented in one study of St. John's Wort, in which patients assigned to St. John's Wort were found to have variable rates of compliance as assessed by blood levels, and the placebo group was found to have a surprising number of participants (17%) with notable St. John's Wort metabolite levels (Vitiello et al., 2005). Study assignment may pose ethical dilemmas. For example, discouraging sedentary control subjects in a study of the impact of exercise on MDD from increasing their exercise is in opposition to established health

guidelines. The popularity of CAM treatments makes it increasingly difficult to find patients who have not had some exposure to the treatments that appear most promising.

Cultural context, diversity in conceptual frameworks of healing practices, and other issues also shape perspectives related to CAM. Randomized controlled trials are not universally accepted as the "gold standard" among CAM practitioners. Culturally valued treatments with long historical use in some cultures often lack a scientific evidence base in published Western literature. Western medicine differs philosophically and conceptually from non-Western systems of medicine, including Traditional Chinese, Tibetan, and Ayurvedic medicine. It exceeds the scope of the task force's mission to broadly evaluate the theoretical underpinnings of various systems of medicine. Instead, we shall focus on the widely used, available CAM treatments that have received some study in RCTs.

OBJECTIVES AND METHODS

Overview of Scope of Work Product: Authors of this paper were invited participants of the American Psychiatric Association's Task Force on Complementary and Alternative Medicine, appointed by representatives of the American Psychiatric Association (APA). The Task Force was charged with developing a report on the topic of CAM for psychiatrists. The Task Force determined that CAM therapies would be assessed for a single treatment indication in which diagnosis and outcome measures could be evaluated. The Task Force selected MDD as the psychiatric disorder of focus due to the relatively large number of clinical trials with CAM treatments and the potential impact on public health. MDD is a prevalent disorder with a substantial global disease burden (Cassano et al., 2002). After consideration of inclusion of a wide variety of CAM therapies, the Task Force selected specific CAM treatments for a final report based on utilization rates, relevance to the treatment of MDD, and public health significance.

Objectives: 1) We evaluated the evidence regarding commonly utilized CAM treatments for MDD with available data from randomized controlled trials. For each therapy, we reviewed efficacy, risks, side effects and drug interactions, general health implications, and treatment recommendations. 2) We also identified the clinical, research, and educational needs regarding CAM in the field of psychiatry.

Methods: Our 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 general risks and benefits. Literature searches included Medline and PsychINFO reviews and manual reference searches. Searches were limited to English language (although manual searches included other languages). Some of the CAM treatments for MDD on which our report focused have been previously reviewed for efficacy (Thachil et al., 2007). We selected treatments for this review based on: 1) the presence of randomized controlled trials in MDD, and 2) widespread use with important clinical safety or health information relevant to psychiatric practice. Finally, we outlined an action plan based on needs pertaining to CAM and psychiatry.

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 (Simopoulos, 1991). The cardiovascular benefits of omega-3 fatty acids include decreased risk of thrombosis and arrhythmias, reduction of triglycerides levels in hypertriglyceridemia, decreased atherosclerosis, reduced inflammation, and modest improvement in hypertension (Kris-Etherton et al., 2003). The American Heart Association recommendations specify that adults should eat

fish at least twice per week, and individuals with cardiovascular disease should consume a supplement of at least 1 g per day of a combination of EPA and DHA (Kris-Etherton et al., 2003). Omega-3 fatty acids may also prevent oxidative damage and cognitive decline associated with aging (Cole et al., 2005; Morris et al., 2005). Epidemiological studies have supported a role for omega-3 fatty acids, generally in the form of seafood intake, in mood disorders. In cross-national analyses, inverse associations have been demonstrated between prevalence rates of major depression, postpartum depression, and bipolar disorders and per capita fish intake (Hibbeln, 1998; Hibbeln, 2002; Noaghiul and Hibbeln, 2003).

Meta-analyses of omega-3 fatty acids for the treatment of mood disorders demonstrate benefits in placebo-controlled trials of unipolar and bipolar depression (Parker et al., 2006; Freeman et al., 2006; Lin and Su, 2007), although heterogeneity of study designs and results has been noted as a methodological concern. Studies vary in terms of omega-3 fatty acids used (eicosapentaenoic acid, docosahexaenoic acid, or the combination), doses, and durations of study trials. Randomized studies with omega-3 fatty acids have generally included small numbers of patients and have utilized omega-3 fatty acids as an adjunctive therapy to antidepressants in patients who still meet criteria for MDD. Peet and Horrobin (2002) demonstrated a benefit of 1 g per day in a RCT (N=70) of 1, 2, or 4 g per day vs. placebo in patients with MDD. Nemets et al. (2003) also found EPA 2 g per day more efficacious than placebo in decreasing symptoms of depression in MDD (N=20). Su et al. (2003) and Silvers et al. (2005) used combinations of EPA and DHA in patients with MDD with differing results. Su et al. (2003) demonstrated a benefit of EPA and DHA over placebo (N=28), while Silvers et al. (2005) did not find a different between omega-3 and placebo groups (N=77).

Few investigators have specifically evaluated omega-3 fatty acids as a monotherapy for MDD. One monotherapy study of DHA (2 g/day) for MDD in 36 adults did not demonstrate benefit over placebo (Marangell et al., 2003), whereas a dose-finding study using three doses of DHA monotherapy demonstrated greater efficacy at 1g/day compared to 2g/d and 4g/day (Mischoulon et al., 2008), consistent with the findings of an RCT of ethyl-EPA as adjunctive treatment in MDD (Peet and Horrobin, 2002). One trial in children demonstrated a benefit of omega-3 fatty acid monotherapy (EPA and DHA) compared with placebo (Nemets et al., 2006). A recent trial 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 (Grenyer et al., 2007). In another recent study, investigators assessed omega-3 fatty acids (1 g EPA) vs. fluoxetine 20 mg daily vs. the combination of the two for MDD in 60 patients (Jazayeri et al., 2008). 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), whereas efficacy data on DHA monotherapy are lacking.

Because of the positive health benefits for mothers and infants, omega-3 fatty acids have received specific study in perinatal depression. Omega-3 fatty acids are crucial for optimal neurocognitive development during fetal development and in infants (Kris-Etherton et al., 2003; Dunstan et al., 2006; Hibbeln et al., 2006). Small RCTs of omega-3 fatty acids (between 26 and 59 subjects per trial) have resulted in mixed findings in pregnant and postpartum women. One trial demonstrated superiority of omega-3 fatty acids (EPA and DHA, 3.4 g per day) over placebo in pregnant women with MDD (N=36) (Su et al., 2008), while two other small trials did not find a difference between omega-3 fatty acids and placebo in samples that included both pregnant and postpartum women (Freeman et al., 2008; Rees et al., 2008).

Side effects of the recommended doses in MDD are relatively minor, and include mild gastrointestinal discomfort, most commonly burping or unpleasant taste (Freeman and Sinha, 2007). Although increased bleeding is a theoretical risk, no actual cases of bleeding have been reported, even in cardiovascular studies of high-dose supplementation in which patients were medically compromised, postoperative, and/or using concomitant anticoagulants (Eritsland et al., 1995; Mueller et al., 1991). However, a case was reported in

which a patient treated with coumadin experienced significant changes in coagulation studies (but no clinical changes) after an increase in dose of concomitant fish oil (Buckley et al., 2004). A subset of individuals with MDD may be at greater risk for comorbid cardiovascular disorders (Fraguas et al., 2007), and the possible mood benefits combined with cardiovascular benefits make omega-3 fatty acids an attractive treatment option to consider. In addition, some psychotropic medications may elevate triglycerides and cholesterol, and contribute to weight gain and other cardiovascular risk factors, making adjunctive omega-3 fatty acids an attractive treatment.

More evidence is required to establish a definitive role for omega-3 fatty acids in the treatment of MDD. At this time, particularly due to the cardiovascular benefits, omega-3 fatty acids are a low-risk augmentation strategy for MDD. Doses of 1-9 grams per day have been studied in mood disorders, with a majority of evidence supporting doses in the lower end of this range, and with specific dose-ranging studies supporting similar efficacy of doses across the range studied (Mischoulon et al., 2008; Peet and Horrobin, 2002). Adjunctive EPA or the combination of EPA and DHA (the combination found in most commercially available brands) appear most useful, with less evidence for DHA alone. The established general health benefits of omega-3 fatty acids, epidemiological evidence for a role in MDD, modest efficacy data, and low risks make omega-3 fatty acids a reasonable augmentation strategy in MDD. An APA subcommittee recommended omega-3 fatty acids as an adjunctive therapy for mood disorders, supported by positive findings in meta-analyses, and in recognition of health benefits (Freeman et al., 2006).

St. John's Wort

St. John's Wort is an herbal remedy that is widely used in Europe. A large number of trials that compare St. John's Wort (usually in the form of hypericum perforatum extract) with standard antidepressants and placebo have been published; however, a lack of a consensus on efficacy for MDD has resulted. A Cochrane meta-analysis (Linde et al., 2005) assessed studies utilizing St. John's Wort for the treatment of MDD, but found heterogeneity in methodology and inconsistency in outcomes. A number of double-blind studies have demonstrated superiority over placebo, although others have not (Shelton et al., 2001; Hypericum Depression Study Group, 2002). 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 (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Of the larger, more rigorous placebo-controlled trials, two that required participants to have Hamilton Rating Scale for Depression (HAM-D) scores of 20 or above at entry did not demonstrate a difference between St. John's Wort and placebo on primary outcome measures (Shelton et al., 2001; Hypericum Study Group, 2002). In the study by Shelton and colleagues (2001), 200 participants with MDD were randomized to St. John's Wort or placebo for eight weeks. The primary outcome was decrease of scores on the Hamilton Rating Scale for Depression (HAM-D), and there was not a statistically significant difference between groups. In the Hypericum Study Group trial (2002), 340 patients with MDD were randomized 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 on HAM-D scores and response rates as determined by both the HAM-D and Clinical Global Impression (CGI) rating scales. The Hypericum Study Group trial (2002) results specifically raise concerns about placebo-response rates and methodology in many treatment studies of MDD, since sertraline, an FDA-approved antidepressant, did not perform better than placebo. However, in other two large trials, investigators did find a significant difference between St. John's Wort and placebo in mild to moderate depression (N=375) (Lecrubier et al., 2002) and a modest, but significant advantage of St. John's Wort over fluoxetine (N=135) (Fava et al., 2005).

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 (including

cyclosporine), antineoplastic agents, anticoagulants (including coumadin), digoxin, oral contraceptives and hormone replacement therapy (Roby et al., 2000; Mannel et al., 2004). Unintended pregnancies have been reported with concomitant St. John's Wort and oral contraceptive use (Schwarz et al., 2003).

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 in the U.S. demonstrated efficacy over placebo. A number of methodological concerns have been put forth with regard to the inconsistent findings of St. John's Wort studies. In newer trials, it is considered possible that several factors contributed to a lack of difference between St. John's Wort and placebo, including recruitment of more refractory patients with depression of greater severity and longer duration, use of subtherapeutic doses of SJW and active comparators, lack of statistical power, and publication bias. Also, it is important to consider that at least half of RCTs of synthetic antidepressants may fail to yield significant differences between the antidepressant under study and placebo. It is therefore not surprising that we see a fairly broad range of results with the studies in question. 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 (SAME)

S-adenosyl-L-methionine (SAME) is the major donor of methyl group in human metabolism. After an initial, serendipitous observation of mood elevation in patients treated with SAME (Pinzello and Andreoli, 1972), Fazio et al (1973) reported "remission" in nearly half of depressed patients in a small open trial of parenteral SAME. In 1975, Agnoli et al (1975) also reported marked improvement of depression in over half of patients given intramuscular SAME. Following these two reports, numerous open studies (Mantero et al, 1976; Andreoli et al, 1977; Salvadorini et al, 1980; Carney et al, 1983; Labriola et al, 1986; Antun, 1987) showed that treatment with parenteral SAME was followed by mood improvement in a substantial proportion of patients. Lipinski et al (1984), using IV SAME in a single-blind study of psychiatric inpatients with depression, reported improvement or remission in 7 of 9 subjects. Antidepressant response was rapid and without significant side-effects.

Of relevance to SAME's putative antidepressant efficacy is the observation by Carney et al (1983) that a small percentage of responders to IV SAME underwent an early switch to mania or hypomania. Further, in an open trial of oral SAME, Carney also reported that a small number of patients experienced 1-3 days of euthymia followed by hypomanic switches (Carney et al, 1987). A highly labile compound, SAME was initially thought to be too labile and polar to survive absorption without giving up its methyl group, and several early clinical studies were limited by the rapid decomposition of the SAME compound administered (Mischoulon and Fava 2002). However, stable oral preparations of SAME were subsequently developed, and the administration of SAME orally was found to be associated with a significant rise of CSF SAME, suggesting that oral SAME is able to cross the blood-brain barrier in humans (Bottiglieri et al, 1990). In a small open trial, Rosenbaum et al (1990) found that non-treatment resistant patients responded to treatment with oral SAME. The markedly significant clinical improvement found in this study following treatment with oral SAME was also accompanied by significant neuroendocrine effects (Fava et al 1990).

Since the original uncontrolled reports, many double-blind studies have been conducted. In these studies, the parenteral doses of SAME ranged between 15 and 1000 mg/day, with most studies using 100-200 mg/day; oral doses of SAME ranged between 400 and 1600 mg/day, with most studies using 800-1600 mg/day. Overall, SAME was generally well tolerated in these studies, and relatively free of adverse effects. There was no apparent hepatotoxicity, and side effects included mild insomnia, lack of appetite, constipation, nausea, dry mouth, sweating, dizziness, and nervousness (Spillmann and Fava, 1996).

Double-blind studies showed that parenteral or oral preparations of SAME, compared with a number of standard tricyclic antidepressants (TCAs) such as clomipramine, amitriptyline, and imipramine, were generally equally effective and tended to produce fewer side effects (Mantero et al, 1975; Scarzella and

Appiotti, 1977; Barberi et al, 1978; Miccoli et al, 1978; Del Vecchio et al, 1978; Monaco et al, 1979; Calandra et al, 1979; Scaggion et al, 1982; Kufferle and Grunberger, 1982; Bell et al, 1988; Janicak et al, 1988; De Vanna and Rigamonti, 1992; Bell et al, 1994; Delle Chiaie et al, 2002; Pancheri et al, 2002). The 2002 meta-analysis of these double-blind trials (AHRQ Publication 2002; <http://www.ahrq.gov>) found no significant difference in outcomes between SAME and conventional antidepressants. The total sample size included in the meta-analysis was 1,015. Similarly, in studies examining the efficacy of IV or oral SAME compared with placebo, SAME was significantly more effective in most studies (Muscettola et al, 1982; Carney et al, 1986; Thomas et al, 1987; Caruso et al, 1987; De Leo, 1987; Janicak et al, 1988; Carrieri et al, 1990; Kagan et al, 1990; Fava et al, 1992; Ancarnai et al, 1993; Salmaggi et al, 1993; Delle Chiaie and Boissard, 1997). The 2002 meta-analysis of these double-blind, placebo-controlled trials (AHRQ Publication 2002; <http://www.ahrq.gov>) found that, in general, SAME was superior to placebo, but improvement was only considered to be a partial response. The total sample size included in this meta-analysis was 422. The results of both AHRQ meta-analyses are consistent with those of a previous meta-analysis by Bressa (1994).

More recent studies, not included in the meta-analyses, also support the efficacy of SAME in the treatment of depression. Two studies by Delle Chiaie et al (2002) and Pancheri et al (2002) have shown that SAME, in both its oral and parenteral formulations, was as effective as imipramine up to 150 mg/day. An open trial by Alpert et al (2004) 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. Gastrointestinal symptoms and headaches were the most common side effects.

One of the issues concerning the oral preparations of SAME in these clinical trials is stability. A compositional analysis (Spillmann and Fava, 1996) of the content of the 400 mg tablets of SAME used by Fava et al in their double-blind trial (1992) showed that tablets, stored for several months, contained the approximately correct molar ratios of adenine and methionine for their labeled weight, but a thin layer chromatographic separation of compounds indicated that more than 50 % of SAME had degraded into a material that probably contained the adenine nucleus and methionine as shown by spectrophotometric analysis, but could not otherwise be identified (Spillmann and Fava, 1996).

The AHRQ (2002) report strongly recommends additional randomized trials. Currently, the first U.S. adequately powered, double-blind, placebo-controlled study in MDD patients of an oral formulation of SAME versus a standard antidepressant is ongoing, sponsored by NCCAM, and the first U.S. adequately powered, double-blind, placebo-controlled augmentation study of an oral formulation of SAME in MDD patients not responding to SSRIs is also ongoing, sponsored by the National Institute for Mental Health (NIMH). In summary, there is good evidence for antidepressant effects of SAME in patients with MDD, particularly as a monotherapy for MDD, with good toleration observed in studies to date.

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 (please see Figure 1 for folate and compounds related to its metabolism). There is consistent and growing evidence of a role for various folate forms in the prevention and treatment of depression, with roles for vitamin B12 and homocysteine currently less well characterized. Studies to date demonstrate efficacy of augmentation

of antidepressants with folic acid (folate), folinic acid (leucovorin), and 5-methyltetrahydrofolate (5-MTHF). Similar findings may be attributable to the fact that these folate forms share an interconversion potential in the complex set of pathways that comprise the one-carbon cycle. These reactions, which in turn depend on B12 and homocysteine availability, are postulated to exert an antidepressant effect by impacting the synthesis of neurotransmitters such as norepinephrine, dopamine, and serotonin. Future research should help to elucidate the relative antidepressant benefits and potential liabilities of each of these folate forms.

The efficacy of folate monotherapy for MDD has yet to be extensively and adequately tested. A few trials have found folate to be effective and well tolerated, although the best dose and form of folate remain unclear. Coppen and Bailey (2000) conducted a randomized trial in which patients with major depression 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. Interestingly, 500 µg/day of folic acid was insufficient to significantly reduce homocysteine levels in men and could partly explain its observed lack of efficacy in men. A higher dose or a different form of folate may be more suitable for antidepressant augmentation in men. 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 (Kelly et al., 2004).

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 (Guaraldi et al., 1993), and patients with comorbid alcoholism and MDD (Di Palma et al., 1994). A sample of patients with dementia and depressive symptoms as quantified by the HAM-D scale experienced significant improvement in depressive symptoms as well as immediate recall compared to a group that received low-dose trazodone (Passeri et al., 1993). Another randomized study 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 (Godfrey et al., 1990). 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 (2002) used leucovorin to augment treatment for MDD in patients who were not folate deficient. The participants had experienced partial or nonresponse to antidepressant treatment. The investigators found a significant reduction in depressive symptoms in the folate group, although only 19% reached remission. Another study of patients with MDD, bipolar depression, and schizoaffective disorder (Coppen et al., 1986) found that folate augmentation enhanced lithium response in patients treated for bipolar and unipolar depression, particularly if they had low folate levels. Patients with higher end-of-trial folate levels experienced a 40% reduction in their affective morbidity. These patients had already responded to lithium when folate was added, which indicates that folate may be effective for reducing residual symptoms. More recently, a preparation of 5-methyltetrahydrofolate (5-MTHF) has been marketed for folate supplementation. This formulation may be more readily absorbed in the brain compared to other folate forms (Mischoulon and Raab, 2007). Studies of this folate derivative for the treatment of MDD are in progress.

Folate and methylfolate monotherapy may benefit certain depressed populations, but more studies are needed. Folate augmentation can also be used to enhance antidepressant efficacy from the start of treatment or, for patients who are already on antidepressant treatment, to convert partial or nonresponders into responders or remitters. Although folate use typically

occurs in the context of low plasma or red blood cell folate levels, individuals with normal peripheral levels of folate may also benefit from folate or methylfolate treatment, especially since peripheral folate levels may not accurately reflect CNS folate levels. Additional studies to determine which forms of folate cross the blood-brain barrier to affect brain levels and to determine efficacious doses are needed. Finally, some studies reviewed here are limited by mixed diagnostic populations (Coppen et al, 1986, Godfrey et al, 1990) or a focus on depressive symptoms rather than MDD in samples with concurrent diagnoses such as dementia (Passeri et al, 1983). Additional investigation is therefore needed to better characterize depressed populations that are most appropriate for folate augmentation, as well as the impact of comorbidity on response to this intervention. While some studies have assessed folate or related treatments in folate-deficient patients, others have not, and at this time patient characteristics of folate responders need to be elucidated. In fact, with many foods supplemented with folate and deficiency likely to become increasingly rare, it will be important to characterize factors associated with response in individuals with normal folate levels.

In summary, at this time, 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 25 years ago (Rosenthal et al, 1984), a large evidence base supporting its efficacy has evolved. In 1998, three of the largest light therapy studies for seasonal affective disorder were published together in the Archives of General Psychiatry (Wirz-Justice, 1998). These papers demonstrated the efficacy of morning light therapy compared with non-light placebo controls (Eastman et al 1998; Terman et al 1998) and evening light administration (Lewy et al 1998; Terman et al 1998). A study group from the American Psychiatric Association published a meta-analysis of light therapy for depression (Golden et al, 2005). 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 to 1.08, $p<0.0001$). This report indicated that the therapeutic effect of light was at least equivalent to and potentially greater than that of antidepressants. This observation was tested by Lam et al (2006), who 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) of 10,000 lux (a unit of illumination intensity) plus a placebo capsule, or dim morning light (100-lux=placebo) plus 20 mg fluoxetine. Both treatment groups improved similarly with no significant differences in response rates (67% for each group) or remission rates (50% for light and 54% for fluoxetine). Post-hoc analysis revealed that the response to light therapy observed after one week of treatment was earlier than that associated with fluoxetine. Although both treatments were well tolerated, the rate of adverse events was lower in the light compared to fluoxetine treated subjects.

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. (2004), which reported a modest antidepressant effect, and by Golden et al (2005), who found an effect size of 0.53 (95% CI = 0.18 to 0.89, $p<0.003$), based on 3 studies. In a third meta-analysis, Even et al (2008) concluded that bright light exposure was not convincingly as efficacious as a monotherapy for nonseasonal depression, with 3 positive and 4 negative studies that met strict inclusion criteria. A noteworthy study is that of Goel et al (2005), who randomly assigned patients with chronic depression (episode duration > 2 years) 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, two small pilot studies in pregnant women with nonseasonal depression demonstrated promising results (Oren et al., 2002; Epperson et al., 2004), but replication with a larger number of subjects is needed.

As an adjunctive treatment to antidepressant drugs for nonseasonal depression, light therapy has demonstrated convincing benefit. In their meta-analysis, Even et al (2008) observed that 4 of 5 studies supported the efficacy of light therapy with antidepressant drugs. The largest RCT to date (Martiny et al., 2005a, 2005b) included 102 patients treated with sertraline (50 mg/day). 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 initial rapid response to light therapy can also be sustained with continuation antidepressant treatment. In 282 patients with seasonal affective disorder (Martiny et al, 2004), responders (62.5% of sample) to one week of light therapy were randomly assigned to citalopram or placebo continuation treatment for 15 weeks. Citalopram treatment (mean dose of 26.3 mg/day) was significantly more efficacious than placebo in sustaining the early response to light.

At both the molecular and behavioral level, information about the impact of light on human affective states and health has grown in the past two decades. Light impacts mood, energy and circadian rhythms, and its therapeutic effects have received attention from the scientific and lay communities (Lamberg, 1998; Wirz-Justice et al, 2004). 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 (Lewy et al., 1987). The phase shift model builds upon evidence across many species that early morning bright light causes biological rhythms to shift to an earlier phase, and that light suppresses the production of melatonin. Neumeister et al (1998) also reported that both tryptophan and catecholamine depletion reversed the antidepressant effects of light therapy, which provided evidence that catecholaminergic systems are involved in response.

The dosing of light therapy has been elucidated in four dimensions: intensity, exposure duration, spectrum and time of day of administration (Terman et al 2005). 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 (Terman et al, 2005) with attenuation of wavelengths <450 nm (which includes far-blue and ultraviolet) and infrared radiation, both of which present ocular risks. The effective broadband white spectrum can vary in color across the range including 3000 Kelvin (K) (soft white), 4000 K (cool white), 5500-7000 K (daylight, or 'full spectrum') and 17,000 K ('blue enhanced'). There is no evidence that the higher color temperatures provide superior antidepressant effect (Terman 2009). Narrow-band blue and green light may also be effective, but data are sparse.

To utilize light therapy, patients sit in front of a downward tilted light box which is situated 12 to 14 inches from their eyes. They can read, eat or 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 early morning as soon as arising from bed. Optimal times for morning exposure have been derived from the Morningness–Eveningness Questionnaire and its correlation with the timing of onset of melatonin secretion. A self-administered test that yields the recommended time for morning light administration is available from the nonprofit Center for Environmental Therapeutics (www.CET.org). To accommodate morning treatment, most patients must wake up earlier than usual. Although light therapy requires a substantial behavioral commitment from the patient, rates of compliance appear to be similar to that of patients who elect antidepressant treatment (Michalak et al, 2007).

The most common side effects of bright light exposure are nausea, jitteriness and headache (Terman et al 1999; Wirz-Justice, 2009). 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 (imipramine, clomipramine, phenothiazine, lithium), supplements (hypericum, melatonin), and other medicines (porphyrin, 8-methoxypsoralen, chloro-quine, hydrochlorothiazide, tetracycline) (Terman et al, 1999).

As with any efficacious treatment for depression, hypomania or mania may occur with initiation of or during bright light therapy. Patients with bipolar depression are vulnerable to mania induction or mixed state development at high light intensity, extended treatment duration, or with early morning light administration (Sit et al 2007; Wirz-Justice et al 2009). Treatment with an antimanic agent concomitant with light therapy is strongly recommended (Sit et al, 2007; Wirz-Justice et al, 2009) to reduce the risk of mania induction. Monitoring for the emergence of manic symptoms is appropriate when initiating any antidepressant intervention.

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. The efficacy of light therapy for nonseasonal depression has been demonstrated in the majority of clinical trials. Study sizes for light therapy have been smaller (approximately 15 to 130 per trial) than for standard antidepressant trials, in large part due to lack of commercial support, and multicenter trials would strengthen the data. Blinding a treatment delivered through the eyes is virtually impossible. Colored or white dim light and inactive negative air ionizers have served as placebo controls that are convincing to subjects. Light intensity and duration manipulations suggest a dose-response function and circadian timing variations have shown reliable differential group effects with morning light superiority.

Light therapy is inexpensive, well-tolerated, amenable to rapid dose changes based upon the effects observed from the previous day, and can be delivered in patients' homes. Given the available efficacy data, it is an underutilized modality for depression care (Wirz-Justice et al, 2004). Recently, an excellent treatment manual has been published for clinicians (Wirz-Justice et al, 2009). At this time, bright light therapy may be a reasonable treatment for MDD, best studied as a monotherapy and less studied as an augmentation strategy. From a safety standpoint, patients should be alerted to possible "switch" to mania or hypomania.

Acupuncture

The evaluation of the efficacy of acupuncture in the treatment of MDD poses many challenges. Some issues include concurrent use of other conventional or CAM treatments, conceptual differences between Chinese and Western medical diagnoses, and the use of disparate acupuncture treatment protocols across studies. Four systematic reviews on acupuncture for depressed mood have recently been published in English language journals (Mukaino et al, 2005; Smith and Hay, 2005; Leo and Ligot, 2007; Wang et al., 2008). Three of these reviews included only English language journals (Mukaino et al, 2005; Smith and Hay, 2005; Leo and Ligot, 2007). Systematic reviews and meta-analyses have demonstrated inconsistent findings regarding efficacy, and an overall lack of adequate studies comparing manual acupuncture and/or electroacupuncture to control conditions such as sham acupuncture or a waitlist control. Participants in treatment studies generally experienced improvement with both active and sham acupuncture. At this time, data are too limited to offer comparison between the efficacy of acupuncture and antidepressant medications. The most recent systematic review conducted by Wang et al. (2008) included Chinese-language publications. Of 200 trials of acupuncture for the treatment of depression, eight small sham acupuncture controlled studies (total N=477) included in the meta-analysis compared manual acupuncture, electro-acupuncture or laser acupuncture with sham acupuncture only. The authors found evidence of beneficial effects of acupuncture in improving the clinical global impression (CGI) score of depressed patients, but heterogeneity of study designs and small sample sizes precluded conclusions about response and remission rates.

In the previously mentioned reviews, authors commented on methodological issues in the study of acupuncture in controlled trials. Absence of agreement on a standardized sham acupuncture protocol that takes into account possible beneficial effects associated with stimulation of specific acupuncture points used as sham points is a challenge. Studies also 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 treatment duration, and lack of follow-up (Leo and Ligot, 2007).

Acupuncture is generally a low risk intervention. Uncommon transient adverse effects associated with acupuncture include bruising, fatigue, and nausea. Serious complications related to acupuncture are extremely rare and include infection with HIV, hepatitis B and C due to use of non-sterilized needles (Vincent 2001). At least two cases of pneumothorax have been reported (Ernst and White, 2001). Adverse events may vary depending on 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. Halbreich (2008) recently assessed systematic reviews of acupuncture and highlighted concerns about disparities between reviews, including only partial overlap between included studies in two reviews (e.g., Smith & Hay, and Mukano et al), in spite of statements that similarly rigorous inclusion and exclusion criteria were used (Leo and Ligot, 2007). Furthermore, re-analysis of Leo and Ligot's review revealed that only one of nine studies included in the review examined the efficacy of single acupuncture points specific to depressed mood using a double-blind sham-controlled paradigm (Allen et al., 1998).

Four papers included in the review (Luo et al. 1985; Luo et al. 1990; Luo et al. 1998; Yang et al. 1994) are in fact summaries of cumulative research findings of investigators at the Beijing Institute of Mental Health, and not independent research studies. Combining observations about the clinical efficacy of acupuncture with findings of sham-controlled trials is questionable. Furthermore, two cited studies (Luo et al. 1998; Roschke et al. 2000) are augmentation trials of acupuncture in combination with antidepressants. Another study (Eich et al. 2000) included in the Leo and Ligot review examined the efficacy of acupuncture in a heterogeneous patient population including patients with severe depressed mood, minor depressive episodes, and generalized anxiety. Another study (Manber et al. 2004) was limited to pregnant women.

When the above studies are excluded on the basis of methodological flaws or heterogeneous study populations, only two well-designed sham-controlled studies remain, both conducted by the same research group (Allen et al. 1998; Allen et al. 2006). One of these (Allen et al. 1998) was a small (N=33) study that found efficacy of individualized acupoints addressing unique clusters of depressive symptoms in moderately depressed women. However, a subsequent study in a larger heterogeneous population (N=151) that included men and women representing a broader age spectrum and a greater range of depressive mood severity, and used the same methods and outcomes measures failed to replicate beneficial effects of acupuncture for depressed mood (Allen et al., 2006). Patients enrolled in both studies were required to meet criteria for a current major depressive episode as defined in the DSM-IV. Exclusionary criteria included: a previous diagnosis of dysthymia lasting longer than 2 years; any Axis I disorder other than major depressive disorder; history of psychosis or mania; substance abuse or dependence within the past 4 months; any on-going treatment; endocrine abnormalities; history of CNS lesions or any medical disorder or treatment that could cause depressed mood; active suicidal risk; and pregnancy. Both studies lasted 16 weeks and consisted of two 8-week treatment regimens. Each 8 week treatment regimen included 12 treatment sessions—2 weekly treatments during the first 4 weeks and one weekly treatment thereafter. In both studies, patients were randomly assigned to one of three groups: a specific "active" acupuncture protocol addressing the unique energetic pattern identified by Chinese medical assessment (e.g., history, pulse diagnosis, and examination of the tongue) as an underlying factor of depressed mood in a particular patient; a non-specific "active" acupuncture protocol targeting legitimate acupuncture points addressing symptoms in a particular patient unrelated to depressed mood; and a wait-list. In both studies, patients in the "specific" group received a total of 16 weeks of treatment aimed at depressed mood. Patients in the "non-specific"

group received 8 weeks of “non-specific” treatment followed by 8 weeks of “specific” treatment,” and wait-listed patients received no treatment during the initial 8 weeks followed by 8 weeks of “specific” treatment. Treatments were individually tailored to each patient’s specific symptom pattern of depressed mood according to a standardized acupuncture manual and were administered by board-certified acupuncturists who believed they were giving valid treatment but were blind to the experimental hypothesis. Ratings by acupuncturists about the perceived efficacy of treatment did not differ between “specific” and “non-specific” treatments, suggesting that acupuncturists were effectively blinded.

Both studies used the Hamilton Rating Scale for Depression (HAM-D) as the primary outcome measure, which was administered by trained raters blind to the intervention condition at intake, mid-study and after the last treatment session. The Beck Depressive Inventory (BDI) was used as a secondary outcome measure and was completed by all patients at weekly intervals. Response was defined as a 50% or greater reduction in HAM-D score and remission was defined as a HAM-D score of less than 7 and, on a patient-to-patient basis, as a 50% or greater decrease in the initial HAM-D score at study end. In the initial study (N=33), symptom reduction in the “specific” treatment group significantly exceeded that of the “non-specific” treatment group on both HAM-D and BDI scores (Allen et al., 1998). On the basis of these response criteria, 50% of patients who received “specific” treatment achieved full remission in contrast to 27% in both the “non-specific” treatment and wait-list groups. By DSM-IV criteria, 42% in the specific treatment group but only 9% in the non-specific group achieved full remission. The researchers viewed these findings as promising but preliminary because of small study size and the fact that the study population consisted primarily of young women. A subsequent larger study (N=151) by the same research group (Allen et al., 2006) found greater decreases in severity of depressed mood in both the “specific” and “non-specific” acupuncture treatment groups at 8 weeks, and inter-group differences were not significant. Eight-week remission rates for the “specific,” “non-specific,” and wait-list groups, were 16%, 33%, and 8%, respectively. At 16 weeks, patients in the wait-list group (who had received the fewest acupuncture treatments) had the lowest symptom severity. Sixteen-week remission rates for the specific, non-specific and wait-list groups were 26%, 39%, and 52%, respectively. A random regression model that examined BDI scores between all subject groups at intake and study completion revealed a significant decrease in depression severity across all subjects but no differences in rate of improvement between groups. A mixed-effects linear regression model was used to determine whether acupuncture had greater efficacy for subjects with particular characteristics, including chronicity of depressed mood, age at onset, current age, sex of the patient, and assessing acupuncturist. No evidence was found to support the hypothesis that acupuncture has relatively greater efficacy for a particular subset of depressed individuals. In the larger study, the researchers also examined acupuncturists’ expectations for the success of the intervention and determined that there was no relationship between HAM-D scores and expectations of acupuncturists. The authors noted that study results could reflect a general lack of efficacy of specific interventions chosen or relatively greater efficacy than predicted for the non-specific intervention chosen to address non-depressive symptoms. They also noted that the success of specific interventions addressing depressive mood symptoms could have been limited if some acupuncturists failed to adequately implement protocols as described in the treatment manual.

Another recently published review of the acupuncture literature noted serious methodological flaws in the systematic reviews of acupuncture studies, including failure to reference excluded studies published in non-English language journals and failure to apply rigorous inclusion criteria for study selection (Derry, Derry McQuay and Moore, 2006). Derry et al (2006) re-interpreted conclusions of systematic reviews of acupuncture studies published since 1996 (including studies on depression) using stricter inclusion criteria and found that none of 35 published reviews showed efficacy for any indication, mainly because not enough patients were enrolled in randomized controlled studies to result in potentially significant findings.

In response to methodological challenges involved in the systematic study of acupuncture and other alternative treatments, some have proposed

consensus methods for the development of standardized protocols for use in future randomized sham-controlled trials on acupuncture (MacPherson H, Schroer S. 2007). 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, 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, data do not suggest that acupuncture is an efficacious treatment for MDD. Although overall risks may be low, rigorous trials to date are lacking that support efficacy.

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. (2006) examined data from 5451 men and 1277 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 (CES-D) and the General Well-Being Schedule, respectively (Radloff, 1977; Fazio, 1977). 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 (BWHs) reported similar findings from an ongoing research study investigating risk factors for major illnesses in adult African-American women (Wise et al., 2006). Vigorous physical activity was associated with a reduced odds ratio (OR) for depressive symptoms.

Exercise has been examined as a treatment for depression, both as monotherapy and as augmentation to antidepressants. Results from two meta-analyses of exercise for depression have been recently published (Lawlor et al., 2001; Sjösten et al., 2006), one of which specifically involved elderly subjects (Sjösten et al., 2006). 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 (i.e., inpatient or home-based exercise) or mode (i.e., 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 (Dunn et al., 2005; Dunn et al., 2002). The investigators used a 2x2 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 two manipulated exercise factors were total energy expenditure and exercise frequency (days/week). High energy expenditure was 180–210 min of exercise per week (consistent with public health recommendations), and was referred to as the Public Health Dose (PHD) cohort. Low energy expenditure was approximately 80 min of exercise per week, the low-dose (LD) group. The two frequencies were 3 and 5 days/week. Participants were randomized into one of five groups that included: PHD over 3 days/week, PHD over 5 days/week, LD over 3 days/week, LD over 5 days/week, or a stretching control group (15 min on 3 days/week). For all conditions, the first 12 weeks of exercise were conducted under supervision, and then 12 weeks of exercise were performed at home or at another facility. The 17-item Hamilton Rating Scale for Depression (HAM-D17) 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. These represent reductions from a mean baseline HAM-D17 score of 16.0 to scores of 8.5, 11.1, and 11.3 for the three groups, respectively. The difference in remission rates between the PHD group and the control group was significant ($p=0.01$). 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 (2007) reported on the SMILE (Standard Medical Intervention and Long-Term Exercise) study, which used a structured clinical interview to examine 202 adults (153 women, 49 men) diagnosed with MDD). Participants were randomly assigned to one of four conditions for 16 weeks: supervised group exercise, home-based exercise, or double-blind sertraline (50-200 mg/day) or placebo pill. The primary outcome measure was the rate of remission (defined as a HAM-D-17 score of <8). Participants randomized to active treatments had nonsignificantly higher remission rates than those receiving placebo (supervised exercise 45%, home-based exercise 40%, sertraline 47%, placebo 31%; $p=0.057$). Similarly, there was no significant differences in HAM-D scores among groups following treatment. These data suggest that the efficacy of exercise may be similar to that of sertraline, although larger, definitive studies are needed.

The vast majority of studies examining exercise as a treatment for depression have investigated exercise as an adjunct to antidepressants. Blumenthal et al. (1999) 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 the Blumenthal study examined the continued efficacy of exercise by conducting a 10-month follow-up from the earlier acute-phase study (Babyak et al., 2000). Patients in the group exercise-alone group had a significantly increased likelihood of remission ($p=0.01$) 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. (1985) assessed 43 patients hospitalized for depression who were receiving individual psychotherapy and occupational therapy, 24 of whom were randomized to aerobic exercise with existing treatment and 19 of whom comprised the control group (no exercise added). Although not controlled for in the analyses, 14/19 in the control group and 9/24 in the exercise group were taking tricyclic antidepressants during study participation. The authors reported a significantly larger difference ($p < 0.05$) in Beck Depression Inventory (BDI) scores between baseline and 9 weeks in the exercise group compared to controls. Similarly, Veale et al. (1992) investigated whether the addition of aerobic exercise would enhance participants' standard treatments for depression in two related, randomized studies involving 124 participants. In the first, subjects either continued their usual treatment (control group) or added three 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 ($p<0.005$), 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 ($p<0.05$). 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 (2001) conducted a pilot study in which 12 antidepressant-treated individuals diagnosed with MDD or bipolar I disorder completed a short-term exercise intervention (30 minutes per day for 10 days). The medications used varied widely and included different types of antidepressants, antipsychotic medications, and lithium. The HAM-D21 and the Scale for Self-Assessment of Depression were used to measure depressive symptoms. Significant differences were found between day 1 and day 10 on both measures.

More recent studies have examined the effect of the addition of exercise for patients with a partial response to antidepressants. In one study aimed at the assessment of exercise adjunctive to antidepressants in older individuals, participants were required to have been taking their medication for at least 6 weeks with no evidence of a sustained response (as defined by a Geriatric Depression Scale score of ≥ 10) (Mather et al., 2002). Eighty-six participants were randomized to attend group exercise classes consisting of weight-bearing exercise performed to music, or health education classes (non-exercise control group) twice weekly for 10 weeks. In both groups, sessions lasted for approximately 45 min. After 10 weeks, 55% (23/42) of the exercise group achieved a HAM-D17 reduction of $\geq 30\%$, whereas only 33% (14/43) of the control group achieved such a reduction. Trivedi et al. (2006a) conducted an open-label pilot study in depressed individuals (aged 20–45 years) with non-psychotic MDD. To be eligible, participants had been treated with an SSRI or venlafaxine for at least 6 weeks with partial benefit, but still experiencing residual symptoms, as indicated by a HAM-D17 score of ≥ 14 at study entry. Eligible participants began a 12-week adjunctive intervention of aerobic exercise (walking or cycling), 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 (baseline mean HAM-D17 score of 17.4). A beneficial effect of the addition of exercise was demonstrated by a mean reduction of 5.8 points in HAM-D17 scores in the intent-to-treat analysis. Improvements in quality of life were also reported. This pilot trial led to the development of the TREAD (Treatment with Exercise Augmentation for Depression) study (Trivedi et al, 2006b), a randomized controlled trial examining SSRI augmentation using a public health recommended dose 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. Study results are currently pending.

The limitations of the available exercise data are important to acknowledge. Studies have consistently demonstrated a reduction in depressive symptoms as a result of exercise treatment. However, many trials examining combination treatment or augmentation of drug therapies with exercise have not adequately controlled for the type, duration, or response to the initial treatment that was combined with exercise. Methodological issues that need to be taken into account include adherence to exercise or control conditions, non-exercise factors that may be associated with a group exercise regimen (such as social contact), and quality of blinding. Finally, clinicians in practice agree that depressed patients often experience difficulties in finding the motivation to participate in exercise programs and physical activity in general. It is therefore possible that depressed individuals who choose to enter exercise clinical trials may have certain characteristics that differ from the general depressed population, and these may impact on 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 three alternative forms of psychotherapies that are not currently considered conventional practice. These were each selected for an

accumulating evidence-base from randomized clinical trials in MDD, and include: 1) mindfulness-based cognitive therapy, 2) problem-solving therapy, and 3) well-being therapy.

Mindfulness-Based Cognitive Therapy (MBCT)

Mindfulness-based cognitive therapy (MBCT) has been developed with the goal of preventing relapses and recurrences of major depressive disorders (Segal, Williams, & Teasdale, 2002). MBCT research is in its early stages, but studies have demonstrated promising efficacy. (Melbourne Academic Mindfulness Interest Group, 2006). MBCT combines mindfulness training (Kabat-Zinn, 1990) with elements of cognitive-behavioral therapy for depression (Beck, Rush, Shaw, & Emery, 1979). MBCT teaches patients to recognize and disengage from negative and ruminative thinking and to access and use acceptance and "being" (Segal et al., 2002). In a recent systematic review by Coelho and colleagues (2007), four relevant studies were identified: 2 RCTs (Teasdale et al., 2000, 2002; Williams et al., 2000), one study based on a subset of one of these trials (Ma & Teasdale 2004), and one non-randomized trial (Kingston et al., 2007). All compared MBCT plus treatment as usual (TAU) with TAU alone. For patients with three or more previous episodes of MDD, two RCTs (Ma & Teasdale, 2004; Teasdale, 2000) reported lower relapse hazard rates for MBCT plus TAU patients compared with the TAU only patients. For patients with two previous MDD episodes, no significant differences between groups were found in the hazard of relapse or recurrence over the study period. A subset of data was reanalyzed by Teasdale et al. (2002) and showed significantly less hazard of relapse or recurrence over the study period for MBCT plus TAU patients compared with TAU only. Like Teasdale et al. (2002), the study by Williams et al. (2000) was based on a subset of data from Teasdale et al.'s (2000) trial. Results from this study showed no significant group by time interaction effect on HRSD scores. However, the MBCT plus TAU group experienced a greater shift away from a cognitive style characteristic of depression. In addition, there were no significant between-group differences in latency to respond or omitting to respond in the Autobiographical Memory Test (Williams & Broadbent, 1986), and there was no evidence to suggest that the results were due to MBCT-specific effects. In a small non-randomized trial, Kingston et al. (2007) found a greater pre- and post-treatment reduction in depressive symptomatology in the MBCT group but no significant between-group differences in change in ruminative thinking.

Evidence from the aforementioned randomized trials suggests that for patients with three or more previous depressive episodes, MBCT has an additive benefit to usual care. However, because of the nature of the control group, these findings cannot be attributed to MBCT-specific effects. Williams et al. (2008) recently reported reanalyses of the two pivotal MBCT trials (Ma & Teasdale, 2004; Teasdale et al., 2000) which reinforced the original findings by Coelho et al. (2007).

A retrospective study was conducted by Kenny and Williams (2007) to examine the effects of MBCT with patients with treatment-resistant depression (TRD), as well as the acceptability and the feasibility of a class format. Seventy-nine patients with treatment-resistant depression participated in MBCT programs as part of routine clinical practice (in addition to standard treatment with antidepressant medication). The results suggested that MBCT is an acceptable and useful treatment for patients who had a partial response to other treatments (i.e., antidepressants and/or standard individual CBT). Furthermore, MBCT appears to be effective in significantly reducing depression scores on clinical scales, even in individuals with more severe MDD, including suicidality. In this study, MBCT was associated with reductions in depressive symptoms, with a large pre-post Effect Size ($d=1.04$). However, a number of methodological limitations (e.g., the lack of a control group) need to be considered. In a recent non-randomized open study of MBCT augmentation of psychotherapy and medication treatment for currently depressed patients with TRD (Eisendrath et al., 2008), a significant decrease in depression and anxiety levels was found for individuals with TRD who received MBCT (using an Intent-to-Treat analysis). Moreover, there was a significant correlation between change in Beck Depression Inventory (BDI) scores and baseline score on the BDI ($r=.49$; $p<.001$). Higher baseline scores were associated with greater

decreases in BDI scores overall. This preliminary study extends the work of others who have begun investigating MBCT for MDD with an emphasis on potential factors of mindfulness and rumination as drivers of the effects (Finucane & Mercer, 2007; Kenny & Williams, 2007).

Problem-Solving Therapy (PST):

Problem-solving therapy (PST) has been examined in several RCTs. There are different types of PST for depressive disorders, including social problem-solving therapy (SPST), PST for primary care (PST-PC), self-examination therapy (SET). Results of thirteen randomized trials of PST have been integrated in a comprehensive meta-analysis conducted by Cuijpers et al. (2007). Most studies found favorable results for PST 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 PST on depressive symptoms, depending on the model of analyses ($d=.34$ in the fixed effects model and $d=.83$ 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 PST (SPST having the largest and PST-PC having the smallest), type of analysis (Intent-to-treat (ITT) analyses resulted in smaller effect sizes) and type of control group (studies with waiting list control groups had the largest effect sizes). These findings indicate that PST has varying positive effects on depressive disorders. More research is needed to ascertain the conditions and subjects in which positive effects of PST are realized. In a recent systematic review by Huibers et al. (2007) of psychosocial interventions by general practitioners, problem-solving treatment has been found to be effective for the treatment of MDD and may be the most promising tools for primary care physicians. However, a stronger evidence-base is required, and the effectiveness of PST in routine practice must be evaluated.

Well-Being Therapy (WBT):

Well-being therapy (WBT) is a specific psychotherapeutic strategy for enhancing well-being, based on Ryff's (Ryff, 1989) multidimensional model of psychological well-being, and encompassing six dimensions: autonomy, environmental mastery, purpose in life, positive relations and self-acceptance (Ryff et al., 1989; Fava et al., 1999). The goal of this short-term therapy is to improve patients' levels of psychological well-being through cognitive behavioral techniques (Fava, 1999). WBT 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 WBT as a sequential method of treatment, based on the use of pharmacotherapy in the acute phase of depression and WBT 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 WBT with CBT or clinical management. At a 2-year follow up, WBT plus CBT treatment resulted in a significantly lower relapse rate (25%) than did clinical management (80%) (Fava et al., 1998). The differential relapse rate was significantly related to the resolution of residual symptoms (Fava et al., 1999). At 6-year follow-up, this WBT plus CBT treatment continued to result in a significantly lower relapse rate (40%) than did clinical management (90%) (Fava et al., 2004). However, these positive results from studies of WBT 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 pharmacological 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 for an adequate trial.

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 standard of care continually evolves in psychiatry, as it does across all fields of medicine. The therapies reviewed in this paper 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 in this area, and the public health significance of the CAM-MDD interface.

In summary, a review of randomized controlled trials for commonly used CAM treatments suggest 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, especially older preparations. Regarding St. John's Wort, which has primarily been studied as a monotherapy, there is greater consensus and support for use in mild to moderate MDD, and less for more severe 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 based on efficacy in randomized controlled treatment trials for MDD, the paucity of treatment studies at this time must be balanced against their low risk of use and important implications for individual and public health. At this time, data do not suggest that acupuncture is an efficacious treatment for MDD. Although overall risks 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 patient adherence to regimens.

Psychiatric disorders are common, and MDD is associated with substantial morbidity and mortality. Available treatments often fall short in terms of efficacy and tolerability, and growing evidence indicates that conventional antidepressants may not be as effective as previously believed (Kirsch et al, 2008; Turner et al, 2008). 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 either over- or under-enthusiasm for categorization as CAM. Individual treatments need to be weighed on the basis of scientific evidence regarding efficacy and safety.

Some of the most promising individual CAM treatments studied for MDD represent modalities that share little other than the almost arbitrary classification of being unconventional practice. However, the essence of what is considered conventional may be arbitrary and nonscientific, and encourages bias regarding approaches to treatment. Therefore, to remain consistent with the field of medicine, we may use the terms "complementary," "alternative," "CAM," and "integrative," but must scrutinize their connotations and semantic limitations.

Treatments or their categorization can evoke a halo of overly positive beliefs and minimization of risks, or, conversely, a skeptically dismissive attitude. Our Task Force operated on the premise that principles of evidence-based medicine apply to the assessment of CAM treatments in psychiatry. CAM therapies must be held to the same evaluative standards as other

treatments for MDD. We advocate for an integrative approach to psychiatric disorders, including conventional and non-conventional evidence-based treatments. Efficacious CAM therapies can crucially expand the "toolbox" of evidence-based therapies we can offer and can engage more patients in treatment.

Our Task Force noted the methodological challenges for antidepressant trials, including high placebo-response rates, difficulty enrolling and retaining participants, and difficulty selecting adequate control conditions for novel treatments. Regarding alternative therapies practiced in frameworks that differ substantially from conventional Western medicine, we acknowledge the ongoing debate over whether standard research methods are applicable and whether elements of treatment can be studied adequately outside the context of the health care system within which they evolved.

Patient preference is an important and poorly understood topic in psychiatric treatment research. Participants in trials of CAM treatments are likely to differ in comparison to those who participate in standard antidepressant trials. Similarly, subjects who participate in psychotherapy trials (considered standard or CAM) probably differ from those who select to enroll in antidepressant trials. Systematic study regarding patient characteristics and decision making about study participation are lacking. In the large, multi-site Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, subjects who did not respond to citalopram monotherapy were offered participation in subsequent protocols, and were able to express whether cognitive therapy would be acceptable in a randomization protocol (Wisniewski et al., 2007). Willingness to accept cognitive therapy was associated with a higher educational level, family history of depression or other mood disorder, and more days in the prior monotherapy antidepressant treatment. Lack of acceptability of cognitive therapy was associated with comorbid panic disorder. We hypothesize that acceptability of participation in studies of CAM treatments would be associated with specific patient characteristics.

The greatest risk of pursuing one of these therapies or other treatments that are under study 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.

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 paper 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.

We support low-risk interventions with benefits for overall health. Of great importance, individuals with MDD are at high risk for medical comorbidity, including cardiovascular disease. Individuals with psychiatric disorders are more likely than the general population to smoke, be obese or overweight, and have diabetes. Advocating exercise, folate/methylfolate, and omega-3 fatty acids as augmentation strategies for MDD supports public health recommendations and are important components of routine treatment planning for MDD. Few patients have contraindications for exercise, and the "prescription" of exercise is likely to result in increased regular exercise in patients, with mood and general health benefits. Folate may play a role in the relief of MDD as a low risk addition to standard treatments, with protective effects against cardiovascular disease in individuals with high levels of homocysteine and the risk of birth defects in pregnant women. Omega-3 fatty acids have well established cardiovascular benefits, and individuals with MDD are known to be at risk of comorbid heart disease as well as other medical conditions that could benefit from modest daily omega-3 fatty acid intake. CAM treatments are not usually included in routine medical or psychiatric training. We encourage inclusion of CAM therapies in medical school, residency, and

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

More research regarding CAM treatments in psychiatry is imperative. Studies must have adequate power to yield definitive data. Appropriate control groups must be considered in study methodology. Funding issues are challenging, since many CAM treatments are not under patent, and industry support is not often available for treatment studies that could have great public health significance. In addition to further rigorous, well powered studies of individual CAM treatments, we encourage studies of comparative effectiveness with CAM compared to standard treatments, as well as further study of individual treatments.

In summary, specific CAM treatments may be low cost, accessible, and have promising efficacy in MDD. Psychiatrists need to understand the data regarding efficacy and risks of commonly used CAM treatments for MDD. Clinical, research, and educational initiatives designed to focus on CAM in psychiatry are clearly warranted.

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