Alternative Treatments for Depression: Empirical Support and Relevance to Women

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Background: This article is a critical review of the efficacy of selected alternative treatments for unipolar depression including exercise, stress management techniques, acupuncture, St. John's wort, bright light, and sleep deprivation. Issues related to women across the life span, including pregnancy and lactation, are highlighted.

Data Sources: Evidence of efficacy is based on randomized controlled trials. A distinction is made between studies that address depressive symptoms and studies that address depressive disorders. The review emphasizes issues related to effectiveness, such as treatment availability, acceptability, safety, and cost and issues relevant to women.

Data Synthesis: Exercise, stress reduction methods, bright light exposure, and sleep deprivation hold greater promise as adjuncts to conventional treatment than as monotherapies for major depression. The evidence to date is not sufficiently compelling to suggest the use of St. John's wort in favor of or as an alternative to existing U.S. Food and Drug Administration–regulated compounds. Initial evidence suggests that acupuncture might be an effective alternative monotherapy for major depression, single episode.

Conclusion: This review indicates that some unconventional treatments hold promise as alternative or complementary treatments for unipolar depression in women and have the potential to contribute to its long-term management. Additional research is needed before further recommendations can be made, and there is an urgent need to carefully document and report the frequency of minor and major side effects.

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Individuals suffering from depression, regardless of gender, often seek alternative treatments.[1] The popularity of these alternative treatments may reflect, in part, the limitations of extant conventional treatments. The prescription of antidepressant medications is the most common treatment for depression, for both women and men. Although a wide variety of antidepressant medications and strategies for the medical management of depression have been developed,[2] antidepressant medications are not universally effective nor are they uniformly acceptable. Approximately 30% to 35% of individuals completing research protocols involving antidepressant medications do not respond to treatment, and the rates of nonresponse are even higher (approximately 50%) for individuals with chronic depression.[3,4] Many patients terminate treatment prematurely because they do not tolerate the side effects associated with antidepressant medications.[5] Even the newer antidepressant medications, which have more favorable side effect profiles than the older agents, are often discontinued because of unwanted treatment-emergent symptoms, such as sexual dysfunction, insomnia, weight gain, and a subjective sense of cognitive and emotional blunting. Rates of dropouts that are attributed to medication side effects are approximately 15% in research studies.[3] In addition, some patients who are otherwise open to taking antidepressant medications may not be willing to do so during specific life stages, such as pregnancy and lactation, and other patients may have comorbid medical conditions for which the use of antidepressant medications is contraindicated.

Psychotherapy is another effective, well-researched, and widely used treatment for depression. In particular, cognitive therapy and interpersonal psychotherapy have efficacy comparable to that of antidepressant medications.[5] Like antidepressant medications, psychotherapy is neither universally effective nor uniformly acceptable. Although the reasons for discontinuing psychotherapy differ from the reasons for discontinuing antidepressant medications, rates of withdrawal from treatment are similar.[3] Moreover, empirically supported psychotherapies for depression are often not available, accessible, or affordable for many patients.

The limitations of these established treatments suggest that those with depression would welcome alternative treatments. In fact, depression is among the most common conditions for which patients seek alternatives to conventional therapies.[1,6] The 2 most common alternative treatments sought for a principal complaint of depression are self-help groups and relaxation,[1,6] but consumer satisfaction is greater for self-help measures such as exercise and diet changes, as evidenced by response to a recent Consumer Reports survey.[7] Two epidemiologic surveys of patterns of use of alternative or complementary therapies[8,9] and 1 survey of users of these therapies[10] focused on mental health and have utilized in-person psychiatric interviews to determine psychopathology. The picture that emerges from these studies is that individuals who report or meet criteria for a mental disorder are more likely to use alternative therapies for any condition than healthy controls and that users of alternative therapies are somewhat less satisfied with the conventional mental health services available to them than are nonusers (20.3% vs. 12.6%).[8] At the same time, it appears that use of alternative therapies specifically to treat the mental disorder is limited. For example, in one survey, only one third of complementary therapy users with self-reported affective disorder actually sought these therapies for their depressive illness.[9]

The popularity of a given treatment, of course, provides no evidence for its efficacy. This article critically reviews studies investigating the efficacy of selected alternative treatments for major depression. This is not a comprehensive review. Instead, it focuses on alternative treatments that were identified in epidemiologic studies to be commonly sought for relief of depression, such as exercise and stress management techniques, and those whose efficacy in the treatment of unipolar affective disorders has been investigated, such as herbal medicine, acupuncture, bright light, and sleep deprivation. This article reviews the evidence for the efficacy and safety of these treatments and discusses issues related to effectiveness, including treatment availability, acceptability, and cost. Issues related specifically to women across the life span are highlighted in the discussion of each treatment modality, when applicable, and the need for evaluating the safety of these treatments during pregnancy and lactation is highlighted. The article concludes with a discussion of directions for future research and methodological challenges associated with the systematic investigation of the efficacy and effectiveness of the treatments covered.

EXERCISE

Evaluation of Efficacy

Despite the fact that over 1000 studies have evaluated the impact of exercise on depressive symptoms,[11] few have examined its efficacy in clinical samples of individuals who met DSM criteria for major depressive disorder (MDD). Similarly, few studies have included a placebo or a no-treatment control. One of these studies focused on older adults aged 50 to 77 years who met DSM-IV criteria for MDD.[12] These patients were randomly assigned to receive a group aerobic program 3 times a week, antidepressant medication (sertraline hydrochloride), or a combination of the two. Pill placebo and no-treatment control groups were not included. Approximately two thirds of the participants were women, and the majority of the sample had a history of recurrent depression. Sixteen weeks of intervention resulted in significant symptom reduction within each treatment group. Sixty percent to 69% of the participants no longer met DSM-IV criteria for MDD at the end of treatment, with no significant differences in response rates across the 3 interventions. Two group differences did emerge: medication produced a significantly more rapid response, and exercise produced lower relapse rates 10 months after remission.[13] Continued adherence to an exercise routine on one's own during the follow-up period was associated with reduced probability of relapse (odds ratio of 0.49). Exercise is reported to have efficacy comparable to that of psychotherapy[14] and to be superior to no treatment.[15] Of particular relevance to this article are 2 controlled studies on the efficacy of exercise intervention for depressive symptoms in women. In one study,[16] 40 young women (aged 18 to 35) meeting Research Diagnostic Criteria[17] for major and minor depression were randomly assigned to 8 weeks of aerobic exercise (running), nonaerobic exercise (weight lifting), or wait-list control. Both exercise conditions resulted in statistically and clinically significant improvement in depressive symptoms compared with the wait-list control condition. Available naturalistic follow-up data indicate that treatment gains were maintained at 1-year follow-up,[16] but no information was provided about the potential contribution of continued exercise past the 8-week acute phase of treatment. Similarly, an earlier study of a nonclinical sample (47 young female college students with Beck Depression Inventory [BDI] scores of 11 or more) demonstrated that aerobic exercise was superior to both relaxation treatment and to a no-treatment control condition.[18] However, exercise does not appear to significantly enhance treatment efficacy in individuals who already receive psychiatric care for depression.[19]

A meta-analysis of 80 studies with mixed methodological qualities and varying type and duration of exercise estimated that the average effect size of exercise interventions when compared with no treatment is –0.53, reflecting a substantially larger drop in depression resulting from exercise than from no treatment.[20] North and colleagues[20] concluded that the exercise effect size increases with increased duration of treatment and that efficacy was independent of age or gender. A more recent meta–regression analysis[21] of randomized controlled trials investigating the effectiveness of exercise on the reduction of depressive symptoms estimated effect sizes for the comparison of exercise with no treatment that are larger than those reported by North and colleagues (–1.1).[20]

Many theories, both biologically and psychologically based, were proposed to explain the antidepressant effects of exercise.[16] These theories are beyond the scope of the present article, but it is worth highlighting the possibility that the antidepressant effects of exercise might be modulated by behavioral and social activation. McNeil and colleagues[15] have directly compared an intervention consisting of 6 weeks of walking exercises with an intervention consisting of social contact in 30 depressed older adults (mean age = 72.5 years). This comparison yielded comparable reductions in depressive symptoms (as measured by BDI scores) that were significantly larger than those observed in the wait-list control.[15] Social activation might be particularly relevant when exercise is performed in a group format or when the intervention targets older adults who might be more socially isolated than their younger counterparts.[12]

Availability, Acceptability, and Cost

Unsupervised and self-initiated exercise is inexpensive, relatively safe, and readily available. The cost increases with increased involvement of professionals, such as a trainer, and when exercise equipment is utilized. Issues of acceptability, motivation, and compliance place some limitation on the utility of exercise as a treatment for depression. In general, group exercise programs are associated with lower attrition (26%)[12] than individual programs (40%).[15,16] Discontinuation rates in individual exercise programs are high even when monetary compensation for participation is contingent on compliance.[16] Reasons provided for discontinuation of exercise treatment include dissatisfaction with the exercise program and logistical difficulties in attending the classes, but not musculoskeletal injury.[12] Although adherence rates among completers of the acute phase of the exercise program were high (70%–90%),[12] rates in nonresearch settings are expected to be lower because the close supervision and the frequent contact with a study coordinator tend to enhance compliance. Moreover, exercise routines may be better suited to some depressed people than others, as such routines are more acceptable to well-educated and healthy individuals.[12]

STRESS MANAGEMENT THERAPIES: MEDITATION, RELAXATION, AND MASSAGE

Relaxation and meditation practices were identified by the Eisenberg surveys[1,6] as the most common alternative treatments sought by individuals with depressive symptoms. There is evidence that relaxation reduces some symptoms of depression, such as anxiety, somatic symptoms, and to a lesser extent depressed mood, but only a few randomized controlled studies have been conducted to evaluate the impact of relaxation and meditation on depressive symptoms of individuals meeting criteria for MDD.

Evaluation of Efficacy

A recent randomized study compared 4 weeks of daily practice of Sudarshan Kriya Yoga (45 minutes each session) with electroconvulsive therapy (ECT) and with imipramine in a sample of 45 hospitalized patients who met DSM criteria for melancholic depression and had Hamilton Rating Scale for Depression (HAM-D) scores of 17 or more.[22] The adaptation of Sudarshan Kriya Yoga that was evaluated in this study consists of 3 sequential periods of rhythmic hyperventilation at different rates of breathing that are interspersed with normal breathing, all performed in a sitting position with eyes closed. The procedure ends with a period of about 10 to 15 minutes of a tranquil state (Yoga Nidra). This study demonstrated equivalent remission rates for yoga practice (67%) and imipramine (73%), both of which were lower than the rate of remission in response to ECT (93%). These results, which are consistent with those from an uncontrolled study of yoga in the treatment of dysthymia,[23] indicate that an intense course of this type of yoga (6 days per week for 4 weeks) practiced in the inpatient environment might be beneficial. It is not clear how well these results would generalize to an outpatient population, to a less controlled environment, or to other types of depression.

Some authors argue that certain forms of meditation, such as mindfulness meditation, might be counterproductive during an acute depressive episode because depressed patients may lack sufficient control of attention to learn the additional attention control skills necessary for meditation.[24] Teasdale et al.[25,26] suggest that mindfulness meditation might, however, be useful in preventing episodes of depression among those who have recovered from depression by other means. These authors argue that mindfulness meditation can teach individuals who have recovered from depression skills of effective emotional processing and that these skills may help prevent relapse.

Support for the efficacy of relaxation methods other than meditation in the treatment of depression is relatively weak. A recent review of complementary treatments for depression[27] identified 3 randomized comparative studies of relaxation in the treatment of moderate depression. The limited data provided initial evidence that relaxation may

enhance the response to pharmacotherapy and that it may be superior to no treatment and to a tricyclic antidepressant. Yet, these results, which were based on small sample sizes, were not replicated, even though the studies were published 10 or more years ago.

Like other forms of relaxation, massage has been reported to decrease anxiety and somatic complaints.[28] The effects of massage on depressive symptoms are more limited. Some studies have documented reductions in self-reported state level of depression immediately following a massage session, but no clinical evaluations of depression severity have been reported. In other words, it is unknown whether the temporary improvement in well-being immediately after a massage session translates into a clinically meaningful reduction in depressive symptoms. Furthermore, most samples that were studied included individuals with depressive symptoms secondary to other psychiatric or medical disorders (e.g., bulimia, nicotine addiction, burn injuries) rather than individuals who met criteria for primary major depression.[28–31] There are only 3 available studies in which the sample consisted of individuals with symptoms of what appears to be primary depression. The first study randomly assigned 32 dysthymic adolescent mothers who recently gave birth to receive massage or relaxation.[32] Ten treatment sessions, twice each week for 5 weeks, produced significantly lower depressed mood scores on the Profile of Mood States (POMS)[33] immediately after a massage session as compared with pre-session depression scores. This immediate reduction of depressed mood was observed both on the first day and on the last day (tenth session) of treatment with massage, but pre-session depressive mood ratings did not decline across the 5 weeks of treatment. Participants receiving relaxation did not report a similar immediate reduction on the POMS depressed mood scale. Relaxation in this study consisted of a combination of yoga and muscle relaxation, taught and practiced in a group format.[32] A similar reduction in depressed mood (measured by the POMS) from before to after a massage session was reported for a sample of 52 hospitalized children and adolescents, half with adjustment disorder and half with depression.[34] Again, pre-session to post-session differences were not observed in the control group, whose participants viewed relaxation videos for 30 minutes each day. The participants who received massage in this mixed sample, unlike the adolescent mothers, did report a significant decline in pre-session depressed mood across the 5 days of treatment. In contrast, no reduction in pre-session depressed mood across time was observed in the control group.[34] A third study targeted older adults with elevated depression scores. Participants received daily massage for 1 month and provided daily massage to infants for 1 month, in a counterbalanced order.[35] Depressed affect was reported to decrease more from providing than receiving massage. Taken together, these data demonstrate that massage provides some immediate increase in subjective sense of well-being for patients who experience depressive symptoms. There is no evidence, however, that massage has long-term benefit or that it benefits patients who meet DSM-IV criteria for a major depressive episode.

Availability, Acceptability, and Cost

Massage, relaxation, and meditation are relatively inexpensive, safe, and accessible. Relaxation and meditation necessitate relatively little contact with a professional after the skill acquisition phase. Unfortunately, the cited studies do not report rates of adherence to or discontinuation from relaxation, meditation, or massage therapies for depression. A likely reason for noncompliance is relaxation-induced anxiety, which occurs in close to one third of individuals suffering from general tension.[36]

ACUPUNCTURE

Acupuncture derives from Chinese medicine. Although depression is not a disease category per se in Chinese medicine, a highly similar condition, neurasthenia, is present in almost 50% of psychiatric outpatients in China,[37] and many of these neurasthenic patients would be diagnosed with MDD according to the DSM. Chinese medicine characterizes conditions in terms of energetic imbalances and views major depression as the result of one or more patterns of imbalance, depending on the precise constellation of symptoms. The correspondence between symptoms of major depression as defined by Western medicine and "patterns of energetic imbalance" as defined by the Chinese medicine diagnostic system is complex,[38] and its discussion is beyond the scope of this article. Traditional Chinese medicine, like psychotherapy, provides a framework for understanding distinct symptom pictures and for developing individualized treatments based on the nature of each individual's particular symptom pattern. The Chinese medicine practitioner therefore designs the treatment based on how each patient is experiencing depression and what precipitating factors—physical, psychological, and social—have contributed to the patient's present condition.

Evaluation of Efficacy

Very few randomized studies have evaluated the efficacy of acupuncture in the treatment of major depression. Only 1 double-blind, randomized, placebo-controlled study of acupuncture as monotreatment for major depression has been published.[39] In this study, participants were randomly assigned to 1 of 3 conditions: a specific treatment designed to treat the energetic imbalance thought to underlie the patient's depression; a nonspecific treatment designed to treat a pattern of disharmony that was not related to the patient's depression, but that was characteristic of the patient; or a wait list. To blind the treatment provider, the specific and nonspecific treatment plans

were developed by an assessing acupuncturist, who followed a standardized manual, and were administered by 1 of 4 other board-certified acupuncturists, who minimized verbal exchange with the participant and refrained from assessing signs and symptoms common in Chinese medicine (pulse and tongue). Acupuncturists were told that the study would evaluate different approaches to treating depression, derived from different theories, and that their task was to implement each treatment faithfully. Because of the fact that any 2 depressed individuals will not have identical symptoms, and therefore not receive the same acupuncture treatment, it is not immediately obvious which treatments are specifically intended to address a particular patient's depression unless the treatment provider performs a comprehensive assessment of a patient's symptoms, which they were prohibited from doing. The success of the strategy was assessed by measuring the acupuncturists' ratings (following the first treatment session) of their expectation regarding the efficacy of the treatment they provided, and the reported ratings were virtually identical for specific and nonspecific treatments.

The success of this blinding strategy can be explained by an analogy between the process by which traditional Chinese medicine arrives at its prescription of points for complex syndromes such as depression and the mathematical concept of a "1-way function." A 1-way function is a mathematical function that is significantly easier to compute in one direction (the forward direction) than in the opposite direction (the inverse direction). It might be possible, for example, to compute the function in the forward direction in seconds, but to compute its inverse could take months or years, if it were at all possible. One-way functions are the basis for many encryption schemes. Like a 1-way function, traditional Chinese medicine provides clear rules to map the set of depression symptoms and their associated patterns of "energetic imbalance" to a set of acupuncture points. At the same time, deciphering from a given set of points precisely what it was mapped from (i.e., what specific constellation of symptoms it is treating) is much more difficult because the number of possible combinations is very large and not unique to depression.

Participants in this double-blind study were 38 women between the ages of 18 and 45 who met DSM-IV diagnostic criteria for current MDD, nonchronic, without psychotic features and who did not meet criteria for any other Axis I disorder. Specific acupuncture treatment produced a significant reduction in symptoms at the end of treatment, and the reduction of symptom severity, independently assessed by a clinical interview and by self-rating, was significantly greater for the specific group than for the nonspecific group. The reduction of depression scores observed in the specific group, however, was not significantly larger than that in the no-treatment control group in this small sample. The determination of whether this finding is simply related to insufficient power awaits the completion of the larger ongoing trial by these researchers. The durability of treatment gains was assessed 6 months after the conclusion of treatment, at which time 24% of patients who remitted with treatment had experienced the redevelopment of a full depressive episode.[40] This figure is comparable to that seen with other treatments.[41] Although the study suggests that acupuncture holds promise in the treatment of major depression, its generalizability is limited by its selective and small sample size that was restricted to young women.

A recent single-blind, placebo-controlled study examined the efficacy of adding acupuncture to the tetracyclic antidepressant mianserin in 70 inpatients with a major depressive episode.[42] Patients received either a valid acupuncture treatment for depression, a placebo acupuncture treatment, or simply continued medication with no additional acupuncture. The specific treatment was administered at a predefined fixed set of points that were not tailored for each patient's presentation of depression. The placebo acupuncture was provided at points adjacent to the valid points of the specific treatment (i.e., at "sham" points). Although patients were blind to treatment condition, treating acupuncturists were not blinded. All patients receiving the combination of mianserin and acupuncture (valid or placebo) improved slightly more on measures of overall function and symptomatology (Global Assessment Scale and Clinical Global Impressions scale) than patients treated with medication alone, but no significant differences emerged between the valid and placebo acupuncture.[42] This study suggests that augmenting traditional pharmacologic treatments with acupuncture may be somewhat helpful in improving overall function, but that such benefit cannot be ascribed to the effect of needling at specific points. On the other hand, acupuncture treatments provided in this study were not optimally effective from the perspective of Chinese medicine because they were not specifically tailored to each patient's symptom picture. Additionally, this study did not evaluate how the addition of acupuncture impacted traditional measures of depressive symptomatology such as the HAM-D or other symptoms that are part of the DSM criteria for MDD.

Several studies conducted in China and the former Soviet Union evaluated acupuncture as a treatment for depression and other psychiatric conditions. Polyakov[43] reported that acupuncture reduced the principal symptoms of depression and lessened the severity and prominence of supplementary symptoms in an open-label treatment of 167 depressed patients. Two other case-report studies found significant improvement of symptoms in patients diagnosed with neurasthenia[44] and other psychiatric presentations involving depressed mood.[45] Two Chinese studies focused on electroacupuncture in the treatment of major depression and found that it produced decreases in HAM-D scores comparable to treatment with amitrip-

tyline.[46,47] Point selection and method of needling varied across these studies. Some included no stimulation, others included manual stimulation, and yet others included electrostimulation. Although far from definitive, taken together, these studies suggest that it might be possible to obtain favorable results using acupuncture to treat mood-related symptoms, including depression, but this hypothesis needs to be directly tested in well-designed controlled trials.

Availability, Acceptability, and Cost

Acupuncture appears to be well tolerated as evidenced by the low dropout rate (13%) reported by Allen and colleagues.[39] This rate compares favorably with the rates reported in studies of antidepressant medications or psychotherapy, which are 25% or more.[3,5] Moreover, the addition of electroacupuncture to imipramine resulted in better tolerance of the medication.[46]

Acupuncture is widely available in the United States, with over 7000 acupuncturists certified by the National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM, http://www.nccaom.org/) and approximately 5000 acupuncturists licensed by the California State Oriental Medical Association (many of which are not licensed additionally by the NCCAOM). Although the cost of acupuncture is lower than that of psychotherapy and antidepressant medication, relatively few insurance companies outside the state of California provide coverage for acupuncture services.

The risks associated with acupuncture in standard practice are minimal. Recent data from a total of 30,338 needle insertions (1441 sessions provided to 391 patients) indicate that standard acupuncture, as practiced in the community, is associated with some mild adverse reactions and that these adverse side effects are transient.[48] The incidence of recorded systemic reactions in individual patients was as follows: tiredness (8.2%), drowsiness (2.8%), aggravation of preexisting symptoms (2.8%), itching in the punctured regions (1.0%), dizziness or vertigo (0.8%), feeling of faintness or nausea during treatment (0.8%), headache (0.5%), and chest pain (0.3%). The incidence of recorded local reactions, expressed as a percentage of needle insertions, was as follows: minor bleeding on withdrawal of the needle (2.6%), pain on insertion of the needle (0.7%), petechia or ecchymosis (0.3%), pain or ache in the punctured region after the treatment (0.1%), subcutaneous hematoma (0.1%), and pain or discomfort in the punctured region during the needle retention (0.03%). Severe adverse events such as pneumothorax, cardiac injury, infection, or spinal lesions are rare when the practitioner is adequately trained and have been classified as provider's negligence.[49] A review of the literature indicates that when hygienic standards are high and acupuncturists are well educated, the risk of adverse events is minimal.[50]

HERBAL APPROACHES

By far the most commonly used, and most widely studied, herbal compound for depression derives from the plant *Hypericum perforatum*, more popularly known as St. John's wort. *Hypericum* is widely used in Europe, particularly in Germany, where it is the most common antidepressant treatment.[51] Its use in North America has recently surged.

St. John's wort contains a variety of compounds, and there is controversy over which of the many compounds provide therapeutic effects. Many studies have used a standardized extract of hypericin. Although it was initially thought that the hypericins were inhibitors of monoamine oxidase (MAO), recent studies challenge this assumption.[52,53] Recent work also suggested that the therapeutic effect may be derived from other compounds within St. John's wort, most notably hyperforin, which enhances the synaptic availability of serotonin, as well as dopamine and norepinephrine.[54] It is possible that no single compound in isolation, but rather the combination of these and other compounds within St. John's wort, is responsible for its therapeutic impact.

Evaluation of Efficacy

A meta-analysis of the efficacy of St. John's wort for depression[55] found that across studies judged to be methodologically acceptable, almost all of which were conducted in Germany, St. John's wort was superior to placebo controls and comparable to standard tricyclic antidepressants. A more recent and selective review, which included several large and methodologically sound trials not included in the cited meta-analysis, essentially corroborates these findings.[56] Although the results of the recent meta-analysis suggest the promise of St. John's wort, the authors note several limitations. The studies included a wide range of patients, measures, and interventions, including some that used St. John's wort in combination with other preparations. The criteria for classifying patients as depressed were not uniform and sometimes only vaguely presented. Outcome measures have seldom involved standardized clinical interviews. Daily doses of total hypericin varied widely across trials, as did the presence or absence of substances other than hypericin that are part of St. John's wort. In addition to the concerns noted by the authors, it is worth commenting that some unblinding of raters might have occurred in studies comparing St. John's wort with traditional tricyclic antidepressants because of the differential side effect profiles of these interventions.

Not included in the meta-analysis or in the review of the literature[55,56] were 2 large-scale multisite, double-blind, randomized controlled trials of St. John's wort that have since been completed[57,58] and several smaller trials reviewed by Maidment.[59] The first large-scale study[57] was a 3-arm study that involved randomly assigning 263

patients to receive either 1050 mg of *Hypericum* extract, 100 mg of imipramine, or placebo. *Hypericum* extract was found to be superior to placebo after 4, 6, and 8 weeks of treatment, producing a larger reduction of depressive symptoms as assessed by the HAM-D and the Zung Self-Rating Depression Scale, and greater reductions in anxiety as assessed by the Hamilton Rating Scale for Anxiety. On all of these measures, *Hypericum* extract was statistically indistinguishable from imipramine. Several other smaller trials published since the 1996 meta-analysis (reviewed by Maidment[59]) reached a similar conclusion. Because this trial compared a relatively high dose of *Hypericum* extract with a relatively low dose of imipramine (selected to be a therapeutic dose that would minimize the side effect profile), it is unclear to what extent *Hypericum* extract would be comparable to typically employed doses of traditional tricyclic antidepressants. By contrast, the second large-scale multisite, double-blind, randomized controlled trial, which involved 200 patients randomly assigned to 900 to 1200 mg/day of St. John's wort extract or to matched placebo pills, found no differences between the 2 groups at any point across the 8-week intervention.[59] The study included subjects with some comorbid conditions and subjects with chronic depression and produced a low rate of response, with 26.5% of those treated with St. John's wort and 18.6% of those given placebo demonstrating at least a 50% reduction in HAM-D score. Similar figures were reported for rates of remission (i.e., HAM-D score 7 or less at the end of treatment), although in this instance, the proportion of participants treated with St. John's wort extract who achieved remission was significantly higher (14.3%) than for those given placebo (4.9%). Consistent with these overall negative results, a recent Consumer Reports survey[7] found that most respondents who had tried St. John's wort thought that it helped little, if at all. This low self-reported effectiveness might in part be related to the heterogeneity in compounds and potency of over-the-counter preparations of St. John's wort and to self-medicating without a systematic and/or adequate dosing regimen.

A third large-scale multisite study, funded by the National Institutes of Health Center for Complementary and Alternative Medicine, is due to be completed in 2002. This trial benefits from its design, which not only involves random assignment to St. John's wort or placebo, but also to the selective serotonin reuptake inhibitor (SSRI) sertraline. There is only 1 published study addressing the comparative efficacy of St. John's wort to an SSRI. In this study of 149 elderly patients, a daily dose of 800 mg of St. John's wort extract was comparable to a relatively low dose (20 mg) of the SSRI fluoxetine in reducing depressive symptoms across 6 weeks as assessed by the HAM-D.[60]

Clearly, further research is required to determine whether St. John's wort may prove effective in the treatment of depression. Specifically, research should ask (1) Does St. John's wort have efficacy relative to placebo across a sufficient number of studies to warrant further investigation? (2) Is St. John's wort as effective as traditional antidepressants? (3) Is St. John's wort effective for a subset of depressed persons? (4) Is it effective and safe in the longer-term treatment of depression? (5) How do different dosages and extracts compare?[61] and (6) What is the interaction between St. John's wort and prescription antidepressant medication and other medications?

Availability, Acceptability, and Cost

Although St. John's wort has become widely available in North America, the content of products labeled to contain St. John's wort varies widely. Extracts from St. John's wort contain at least 10 compounds that may contribute to its pharmacologic effects,[62] only 1 of which is hypericin. Most products available on retail shelves—as well as those used in clinical trials—are standardized on hypericin content, but vary with respect to the other compounds. Additionally, because there is no independent agency currently overseeing the purity and potency of herbal products sold in North America, 2 products purporting to have similar concentrations of hypericin may in fact have different concentrations of hypericin and will almost surely have different concentrations of other compounds. Similarly labeled products therefore cannot be assumed to have equal pharmacologic or therapeutic effects. Caveat emptor is advisable.

In terms of cost, St. John's wort is substantially less expensive than traditional antidepressant medication. Based on prices found at a large national drug store chain, a daily dose of 900 mg of St. John's wort extract (standardized to 0.3% hypericin) is about half the cost of a 100-mg daily dose of imipramine and about one tenth the cost of a 20-mg daily dose of Prozac (fluoxetine). A comprehensive and systematic evaluation of side effects of St. John's wort is required and has yet to be conducted.

St. John's wort has been used safely for large numbers of people in Germany, and the published clinical trials have uncovered no serious dangers from St. John's wort per se. In particular, there appear to be no significant adverse effects on cardiac conduction.[63] Side effects of St. John's wort may include photodermatitis, gastrointestinal tract upset, dizziness, dry mouth, sedation, restlessness, constipation, and headache,[59,62] but the number of premature treatment terminations because of adverse side effects is lower than for tricyclic antidepressants.[55] Only 1 study compared the side effect profiles of St. John's wort and an SSRI.[60] It found that the frequency of adverse side effects was comparable for the 2 treatment groups.

There have been case reports, however, of adverse effects of St. John's wort when used in conjunction with other medications. As a result, the National Institute of Mental Health has recently issued a public alert for people

to avoid taking St. John's wort if they are taking indinavir (a protease inhibitor used to treat human immunodeficiency virus), cyclosporine (used to reduce the risk of organ transplant rejection), or the cardiac-related medications digoxin and warfarin. Additionally, combining St. John's wort with an SSRI could possibly result in serotonin syndrome, as was recently observed in 5 elderly patients.[64] St. John's wort has also been reported to lead to decreased bioavailability of some drugs (e.g., digoxin, theophylline, cyclosporine, and phenprocoumon)[65] and increased metabolism of other drugs, including cyclosporine, indinavir, and, relevant to many women, oral contraceptives.[66] When St. John's wort was thought to be an MAO inhibitor, some practitioners advised people to avoid food and beverages high in tyramine (since the interaction of MAO inhibitors and tyramine can cause a rapid and uncontrolled episode of hypertension). The more recent findings that St. John's wort is not a potent MAO inhibitor, and the fact that many people in Germany have tolerated St. John's wort without dietary restriction, suggest that dietary restriction is not a necessary precaution when taking St. John's wort. On the other hand, there would be no harm in reducing intake of tyramine-laden foods until the controversy around MAO and St. John's wort is resolved.[51] It is also worth cautioning against combining traditional antidepressants with St. John's wort. Finally, pregnant and lactating women are generally advised not to take St. John's wort even though no direct evaluations of the safety of St. John's wort during pregnancy and lactation have been conducted.[67]

LIGHT THERAPY

Evaluation of Efficacy

There is a large body of literature demonstrating the efficacy of light therapy as a treatment of seasonal affective disorder.[68,69] One study further demonstrated that the observed therapeutic effects of bright light exposure cannot be attributed solely to expectation.[70] Efficacy appears to be comparable to that of the antidepressant fluoxetine.[71] Although treatments vary across studies in terms of the timing of the light exposure (evening versus morning), the duration of each exposure, and the duration of treatment, it appears that 1.5 to 2 hours of treatment daily over 4 to 5 weeks produces good therapeutic results, with slight, but not robust, superiority for morning light exposure relative to evening exposure.[70,71]

While effective for the treatment of seasonal affective disorder, phototherapy is significantly less effective for the treatment of nonseasonal MDD.[72,73] One controlled study compared the effects of bright light and dim light exposures in patients with unipolar nonseasonal depression and found slight reduction in depression scores with 1 week of exposure to both the active treatment, bright light, and to the placebo, dim light, with no significant difference between the 2 treatments.[74] In contrast, another study found that participants exposed to bright light had a significantly greater improvement in a global depressive score than those exposed to dim light.[75] A literature-based comparison between the effects of bright light exposure and pharmacotherapy concluded that light therapy produces faster antidepressant benefits than psychopharmacologic treatment[76] but, to date, there have been no direct randomized comparisons between bright light and medications for nonseasonal unipolar depression. There are also no data on the efficacy of bright light treatment beyond 1 or 2 weeks, nor are there data concerning the degree to which the limited benefits of brief light therapy are maintained over time. In the absence of data on these important issues, the clinical utility of bright light exposure in the treatment of unipolar nonseasonal depression remains limited. Initial evidence suggests that augmenting standard treatment for nonseasonal depression with bright light exposure during the winter may be beneficial,[77] but this possibility needs further empirical investigation. Light exposure might also be useful in the maintenance of gains following standard treatment for depression, but this possibility too awaits further research. There are some indications, based on small sample sizes, that bright light might be effective for the treatment of premenstrual dysphoric disorder and postpartum depression.[78–80]

Availability, Acceptability, and Cost

Light therapy, although generally safe, is not tolerated by all individuals. Side effects of light therapy include hypomania, present even in nonseasonal unipolar disorder,[75] jumpiness/jitteriness that is more pronounced with morning light exposure, headache, and nausea.[81] Prevalence rates of these side effects are estimated to range between 8% and 16% following treatment with 10,000 lux.[81] Bright light therapy might be less acceptable than antidepressant medication as evidenced by larger dropout rates.[71] The cost of treatment involves the cost of a light box ($200–$400) and the cost of consultation with a qualified health professional with knowledge and experience in delivering this intervention. At present, relatively few health care providers are sufficiently trained to provide treatment.

SLEEP DEPRIVATION

Evaluation of Efficacy

A large and consistent body of literature documents the rapid and profound positive effects that a single night of total sleep deprivation has on depressed mood. Peak benefits are usually observed in the afternoon following the night of sleep deprivation. This positive impact of sleep deprivation on depression is opposite to its effects on healthy nondepressed individuals. The improvement in mood is observed in 60% of all patients with affective

disorders,[82] with higher rates among patients with melancholic unipolar depression[83]; those with diurnal mood variability, particularly those whose mood is worse in the morning[82]; and those with a single episode of depression.[84] The clinical utility of sleep deprivation, however, is quite limited, because the improvement is transient and usually dissipates after a night of recovery sleep. Prolonged sleep deprivation is not only impractical but also leads to worsening of mood.[85] There are some indications, however, that even a single night of sleep deprivation may speed therapeutic response among those treated with antidepressant medications[86] and that bright light exposure can prolong the therapeutic effects of sleep deprivation.[87,88]

Availability, Acceptability, and Cost

Sleep deprivation is not well tolerated, and dropout rates from protocols that require multiple nights of sleep deprivation are high.[89] Worsening of symptoms is reported in depressed individuals with psychotic features[84] and in bipolar depression.[90] Should future research support the utility of sleep deprivation in speeding the response to antidepressant medication and in the treatment of individuals with treatment-resistant depression, sleep deprivation might become an inexpensive and easily accessible complementary treatment for nonpsychotic unipolar depression. Initial evidence suggests that partial sleep deprivation might benefit women whose depression began during pregnancy or during the year after delivery.[91]

ALTERNATIVE TREATMENTS DURING PREGNANCY AND LACTATION

During pregnancy and lactation, depressed women are often reluctant to take antidepressant medications. It is generally agreed that drugs, including antidepressants, should be taken during pregnancy only when obtaining no treatment poses a greater risk to the mother and the fetus than taking the drug.[92] When untreated, depression during pregnancy has significant deleterious effects, including low infant birth weight, preterm delivery, small infant size relative to gestational age, infants that are difficult to console,[93–96] and postpartum depression.[97] It is therefore important to identify safe and effective treatments for depression during pregnancy. With the exception of partial sleep deprivation,[91] there has been no systematic evaluation of the safety of the alternative treatments discussed here during pregnancy. Absence of safety data is particularly alarming for herbs, given the common tendency to equate "natural" with "safe." There is an ongoing study (sponsored by the Agency for Healthcare Research and Quality) testing the efficacy and evaluating the safety of acupuncture as a treatment for depression during pregnancy. The acupuncture protocol of this ongoing study has been modified so that it does not permit the use of acupuncture points that have been classified in Chinese medicine textbooks as forbidden during pregnancy as well as points that are identified as requiring extra caution when administered.

DISCUSSION

This review clearly indicates that some unconventional treatments hold promise as alternative or complementary treatments for unipolar depression and have the potential to contribute to its long-term management.

Exercise and stress reduction methods hold greater promise as adjuncts to conventional treatment than as monotherapies for major depression. There is evidence that exercise improves mood, but observed effect sizes in studies of its efficacy as a treatment for major depression are smaller than those observed for antidepressant medications or for psychotherapy. Moreover, issues of motivation, adherence, and persistence may limit the role of exercise in the treatment of major depression in the community. Future research should, therefore, focus on these practical limitations, and ways to increase motivation and commitment, such as the integration of psychotherapy and exercise, need to be evaluated.

Stress reduction methods, with the possible exception of Sudarshan Kriya Yoga, are not effective for treating major depression. Nevertheless, stress reduction methods may be useful adjuncts to empirically supported treatments for depression because they can effectively reduce the anxiety that is often an associated symptom of depression. Research needs, therefore, to focus on exploring what the role of stress reduction methods in the management of depression should be. For example, stress reduction methods could be useful along with conventional treatments during the acute phase of treatment, or when added later to treat residual anxiety symptoms following an adequate trial with a conventional method. Stress reduction therapies might also play a role in prevention of major depression in individuals who are at risk, such as those with personal or familial history of the disorder.

There is initial evidence from 1 double-blind controlled study that acupuncture might be an effective alternative monotherapy for major depression. If this finding is replicated and if acupuncture is further shown to remain safe and effective during pregnancy and lactation, acupuncture could become the treatment of choice during these sensitive periods. In addition to continued testing of the efficacy of acupuncture relative to control, future research will need to compare the efficacy of acupuncture with that of conventional treatments and investigate how the treatment protocols used in clinical trials might best be disseminated to treatment providers in the community.

Empirical support for St. John's wort as a monotherapy for major depression is mixed. Differences between studies may be attributed to differences in sample characteristics, such as disease severity, chronicity of the depressive

illness, and the presence of comorbid conditions. The evidence to date is not sufficiently compelling to suggest the use of St. John's wort in favor of or as an alternative to existing U.S. Food and Drug Administration–regulated compounds. Further tests of the efficacy of St. John's wort in general and potential differential efficacy in specific subgroups of patients are necessary. Future research will also need to focus on determination of what constituents of St. John's wort are responsible for any potential therapeutic effect. There is a need for continued evaluation of the safety of St. John's wort in general and during pregnancy and lactation, and for ways to bridge the gap between the results of the clinical trials and the instantiation of St. John's wort as a treatment for general use.

Neither bright light exposure nor sleep deprivation is likely to become a useful alternative monotherapy for major depression: bright light therapy is ineffective for nonseasonal depression, and the benefits of sleep deprivation are transient. Nevertheless, these unconventional treatments could play a role in speeding response to pharmacotherapy, and they might be useful as adjunctive components in the management of treatment-resistant depression.

Safety Issues

Evaluation of safety is of particular relevance to alternative therapies because there is a prevailing misconception that just because something is "natural" or "used for centuries," it is safe. Adhering to the "first do no harm" principle dictates that all research on alternative treatments for depression carefully document and report the frequency of minor and major side effects. Effects reported should also include secondary side effects, such as involvement in an automobile accident secondary to severe sleepiness that could have resulted from sleep deprivation, or losing one's job after an injury sustained during exercise.

Future Directions

It is clear from this review that many questions need to be answered before the promise of alternative treatments can be actualized or dismissed. These questions can be categorized into 3 sets. The first set is related to establishing efficacy and safety in a clinical sample of patients with major depression. Does a given alternative treatment provide significant benefits beyond those offered by placebo and nonspecific therapeutic factors? Are these benefits comparable to those obtained by conventional treatments? How long are the benefits retained? Benefits should be assessed both in terms of clinical significance (percentage of patients with meaningful response) and in terms of statistical significance (change on a continuous measure of depression severity).

A second set of questions is related to optimizing treatment. What is the optimal frequency and duration of treatment necessary for therapeutic response? How should treatment gains be consolidated and maintained? What is the optimal strategy for relapse prevention? What is the impact of adding an alternative treatment to an existing conventional therapy, either concurrently or sequentially? (For example, what combinations of conventional and unconventional treatments improve outcome? Do some combinations actually decrease efficacy of either single modality? What combinations are safe?) What aspects of outcome are impacted by specific combinations of conventional and unconventional therapies? (Possible aspects to consider include rates of response, magnitude of response, course to response, adherence, side effect profile, and rates of relapse and recurrence.) Can unconventional therapies, such as relaxation, meditation, or acupuncture, be used in individuals with incomplete remission following a conventional treatment?

A third set of questions relates to effectiveness. Will positive results from efficacy studies generalize to community settings? For example, is it possible to motivate depressed patients to consistently engage in an exercise program outside the context of a research protocol? Can acupuncture methods that were standardized and empirically validated be effectively disseminated and adhered to outside the controlled research environment? Should St. John's wort be regulated? How can the combination of conventional and unconventional treatments be provided in a coordinated and integrated manner?

Methodological Issues

There is a rich literature on methodological issues faced by treatment outcome research in general and for depression in particular. This literature highlights the importance of periodic assessment with standardized outcomes that include both self-report measures and structured clinical interviews and the importance of assessing not only change in depression severity but also response, relapse, and recurrence. Many other general methodological issues that are relevant to the study of the efficacy and effectiveness of any treatment for depression, including alternative treatments, will not be expanded here. Instead we will focus on 1 central issue: identifying adequate control groups for the target treatment. The choice of control can be guided by answering the following 2 important questions: (1) Is the target treatment more effective than an inert treatment or no treatment? and (2) Are specific factors contributing to its efficacy above and beyond the nonspecific factors?

A wait-list (delayed treatment) group provides control for spontaneous remission and for the potential therapeutic effects of the attention provided to patients by the research process itself. Wait-list has been commonly used as control in psychotherapy outcome research and can be easily implemented in testing efficacy of alternative treatments for depression. Choosing an inert (vis à vis depression) treatment is a challenging task that has eluded psychotherapy outcome research and has just begun to be addressed in research on the efficacy of alternative treatments

for depression. Ideally, an inert treatment should share some nonspecific factors with the target treatment (e.g., amount of and nature of interaction with the treatment provider) and should not produce significantly better outcome than either a standard placebo treatment for depression or no treatment. Because nonspecific factors—such as expectations of benefit, activation, and interaction with a caring provider—play such an important role in the treatment of depression, it is difficult to find a control treatment that shares these nonspecific factors with the active treatment and yet remains as ineffective as no treatment. Therefore, it is recommended that studies include both a wait-list (or delayed treatment) control and a pseudo-inert treatment that controls for expectations, attention, and other anticipated nonspecific factors. It is also important to include an assessment of expectations both before treatment begins and shortly after its initiation to allow for statistical control of its impact on outcome. For example, a treatment consisting of social activation of depressed older adults[15] is a good pseudo-inert control for group exercise as the target treatment, because it shares a number of nonspecific factors with the target treatment. These include patient expectations, level of social contact with other patients, level of contact with research personnel, and the passage of time. It differs from the target treatment in level of physiologic activation and in fitness training, 2 factors that are presumed to be involved in reducing the target symptom. Another example is light Swedish massage as a pseudo-inert control for acupuncture. The two share the following nonspecific factors: attention, similar frequency and duration of interaction with a treatment provider, minimal verbal interaction with a treatment provider, physical touch, expectation, a general relaxing effect, and respite from daily stress. The problem with these 2 examples is that they cannot be delivered in a blind manner, since both patient and provider know exactly what treatment is being delivered. Although the issue of blinding can be addressed to some degree by blind assessments of outcome, it is nevertheless best if treatments can be provided in a double-blind manner so that subtle influences by the treatment provider can be avoided. A good example of a pseudo-inert treatment is the standardized nonspecific acupuncture treatment used by Allen and colleagues,[39] discussed earlier in this article.

CONCLUDING REMARKS

The widespread use of alternative treatments, many of which are untested or only incompletely tested, creates an urgent need for careful research examining the efficacy, effectiveness, and safety of these various treatments. As is the case with all novel treatments, some will make their way into the mainstream of treatment approaches, while others will find their place in history books next to snake oils and mesmerism.

Drug names: amitriptyline (Elavil and others), cyclosporine (Sandimmune and others), digoxin (Lanoxin and others), fluoxetine (Prozac and others), indinavir (Crixivan), sertraline (Zoloft), warfarin (Coumadin and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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