Complementary and Alternative Medicine Therapies in Mood Disorders

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Abstract and Introduction

Abstract

This article reviews the potential uses of complementary and alternative medicine (CAM) techniques for individuals with mood disorders. Mood disorders are among the most prevalent mental health issues today and there are many approaches towards their management. While many different types of medication are available, more and more people turn to CAM interventions to help manage their mood disorders. CAM interventions can include herbal remedies, acupuncture and meditation. There is an increasing number of research studies on CAM intervention in mood disorders, and this article critiques such data and attempts to provide a clinical perspective within which these CAM interventions might be considered.

Introduction

Mood and anxiety disorders, which include a broad range of diagnoses, such as major depression, dysthymia and others, pose a significant public health burden on society because of their high prevalence rates[1] and associated morbidity, mortality and healthcare costs.[2–4] Despite the availability of many conventional treatment options, epidemiological studies have shown that only a minority of individuals with these disorders seek mental health treatment.[5] Several studies have shown that the prevalence of mood and anxiety disorders is higher than that of any other chronic medical condition.[6] Data from the WHO Composite International Diagnostic Interview (CIDI),[7,8] demonstrated that more than a third of respondents typically met criteria for a lifetime CIDI disorder.[8] More concerning, survey-specific treatment questions showed that most mental disorders were untreated.[9,10] While secondary analyses of some of the CIDI surveys concluded that up to half of 12-month mental disorders were mild and found that treatment was consistently correlated with severity, between a third and two-thirds of serious cases in these surveys received no treatment.[10,11] In addition, studies show that the unmet need for treatment is greatest in traditionally underserved groups, including elderly persons, racial–ethnic minorities, those with low incomes, those without insurance and residents of rural areas.[12–15] This is particularly troubling because mood disorders can have a greater impact on daily functioning than many serious chronic physical illnesses.[16]

There is evidence that a subset of individuals with depressive symptoms will seek nonconventional treatment with complementary and alternative medicine (CAM).[17] CAM treatments are now widely available and have increased in use in recent decades. The 2007 National Health Interview Survey (NHIS), which included a comprehensive survey of CAM use

by Americans, demonstrated that almost 40% of adults use CAM.[18] Americans with depression are more likely to use CAM remedies than conventional antidepressants (ADs) or psychotherapy,[19] and symptoms of depression, anxiety and insomnia are among the most frequently cited reasons for CAM use.[19] A meta-analysis that assessed patient characteristics in randomized controlled trials (RCTs) of CAM therapies versus conventional AD for major depressive disorder (MDD) found no clinical variables, including severity of depression at baseline, to differ between CAM and standard AD trials, although there was a significantly higher proportion of women in the CAM trials than in standard AD trials.[20] This is consistent with surveys that indicate a more prevalent use of CAM therapies among women.[18,21] Many individuals taking conventional AD therapy either augment their treatment with a CAM therapy or switch to CAM remedies owing to medication-induced adverse effects, incomplete response to conventional treatment, cost or a desire to control their own treatment.[22–25] There is some evidence that individuals seeking CAM treatments often come from vulnerable populations, such as the uninsured or racial and ethnic minorities.[26–28]

This article provides an overview of currently available data on commonly used CAM treatments for depressive mood disorders. CAM interventions include a broad range of healing modalities and practices and the boundaries between CAM and allopathic healthcare domains are not always clearly defined or fixed.[29] However, in general, CAM remedies include those practices that are thought to be outside of the dominant or conventional medical and psychological approach. The National Center for Complementary and Alternative Medicine classifies CAM modalities/practices into four broad categories (although a modality/practice can belong to more than one category): natural products; mind–body medicine; manipulative- and body-based practices; and other CAM practices. In this article, we will focus on the practices that have been most widely evaluated in the management of patients with mood disorders.

Natural Products

This category includes a variety of botanical medicines, vitamins, minerals and other natural products. In a survey of CAM use from 1997 to 2002, the use of botanical remedies for depression rose from 12.1 to 18.6%.[30] In another survey of over 2000 adults in the USA, 53.6% of respondents with depressive symptoms reported using CAM therapies within the preceding 12 months, with botanical or herbal therapies near the top of the list.[1] Remedies that have a reasonable data base include hypericum (St John's wort), *S*-adenosylmethionine (SAMe), tryptophan (TRP)/5-hydroxytryptophan (5-HTP) and omega-3 fatty acids, all of which are reviewed below. Some other commonly used CAM remedies with more limited evidence base include folic acid, *Lavandula angustifolia*, *Ginkgo biloba*, *Rhodiola rosea* and *Crocus sativus*.

Hypericum Perforatum (St John's Wort)

Several constituents of hypericum are thought to exert an AD action, particularly hypericin and hyperforin, although a combination of several of the plant's naturally occurring compounds may better account for its activity.[31] The herb has been shown to inhibit monoamine reuptake and downregulate monamine receptors in the brain.[32] A recent meta-analysis of 37 double-blind RCTs with hypericum (of which 26 were placebo-controlled and 14 were compared to a conventional AD) found inconsistent results.[33] While hypericum was generally superior to

placebo, it was only equivalent to conventional AD therapy for mild depression. For example, a 6-week, placebo-controlled study of hypericum versus citalopram in mild-to-moderate depression, found noninferiority of hypericum versus citalopram, while hypericum and citalopram were both superior to placebo (with hypericum showing a superior tolerability profile compared to citalopram).[34] Another 6-week, multisite RCT compared hypericum to placebo in 332 patients with mild-to-moderate depression, and found that hypericum resulted in a significant reduction in depression ratings versus placebo.[35] A 4-week, multisite RCT of hypericum versus fluoxetine or placebo in 163 patients with mild-to-moderate depression found no superiority of either treatment versus placebo, with the possible exception of a greater remission rate with hypericum (24%) and fluoxetine (28%) versus placebo (7%). Hypericum was significantly better tolerated than fluoxetine.[36] Other comparisons between hypericum, fluoxetine and placebo show conflicting results.[37,38] However, hypericum has better tolerability and substantially lower incidence rates of adverse events than conventional ADs,[39] and tolerability is frequently cited as an important motivator for individuals turning to CAM interventions versus conventional medical ADs. Nonetheless, photosensitivity is observed in large doses, and the herb induces cytochrome P450 enzymes. This can cause decreased absorption and increased clearance of drugs, including antiretrovirals, benzodiazepines, oral contraceptives, digoxin, phenobarbitol and theophylline.[40] There may also be an increased risk of toxic interactions with a number of ADs, resulting in serotonin syndrome.[41]

S-*adenosyl-methionine*

S-adenosyl-methionine is an amino acid that is the major donor of methyl groups needed in the synthesis of monamine neurotransmitters (dopamine, norepenephrine and serotonin) and membranes, and is distributed widely throughout the brain. It is commonly made commercially through a yeast fermentation process. It is widely prescribed in Europe as a CAM AD, and is gaining popularity in the USA. Preclinical studies suggest that SAMe levels may be reduced in MDD.[42] Double-blind studies suggest that SAMe was equally effective as a number of standard ADs and tended to produce far fewer side effects.[43] While one review of 14 RCTs (six with a tricyclic AD [TCA] comparator) advised caution and concluded that any consideration of SAMe as a clinically significant AD therapy was premature because of methodological shortcomings and modest effect size,[44] another meta-analysis by the Agency for Healthcare Research and Quality, which examined 28 studies, concluded that SAMe was clinically and statistically superior to placebo, and that were no significant differences in outcome between SAMe and conventional ADs.[45] A recent review of 11 SAMe studies, using change in depression ratings as the primary outcome measure of effect size, concluded that SAMe produced a significant effect versus placebo.[46] Furthermore, a recent study demonstrated that SAMe actually enhanced the effectiveness of serotonin reuptake inhibitors in patients who were originally nonresponders.[47] Adverse effects are generally mild and include insomnia and gastrointestinal problems. However, there are a few reported cases of the induction of mania from SAMe treatment,[48] and antiparkinsonian medications may be less effective when patients are also taking SAMe.

Omega-3 Fatty Acid

Omega-3 fatty acids are essential fatty acids (EFAs) that play a role in maintaining brain structure and function by stabilizing neuronal membranes and facilitating monoamine

neurotransmission.[49,50] The human body is unable to synthesize EFAs. Thus, they must be acquired in food or as dietary supplements. The primary EFAs are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The most common source of EPA and DHA is fish oil. Some plants, such as flax and hemp, are sources of α-linolenic acid, a fatty acid that converts into EPA and DHA. Most of the currently available data is on EPA and DHA from cold water fish.

Studies have demonstrated that reduced levels of EFAs may be associated with depression,[51] and that EFA supplements may enhance mood.[52] One study comparing combination EPA/DHA versus placebo (as adjunctive therapy) in 28 MDD patients found EPA/DHA to produce a greater reduction in symptoms ratings (compared to placebo).[53] Another 4-week RCT found EPA 2 g daily to be an effective adjunctive therapy in 20 MDD patients with incomplete AD response.[54] Although the heterogeneity of study designs and results have been noted, in general meta-analyses of omega-3 fatty acids for the treatment of mood disorders demonstrate benefits in placebo-controlled trials of unipolar and bipolar depression.[55,56]

Other CAM Products

There are several other CAM products that are used for mood disorders, but most have little or no supportive data yet. A few have had some supportive evidence, such as TRP and 5-HTP, both of which are amino acid precursors of the neurotransmitter serotonin. An evidence-based review of 108 TRP and 5-HTP trials suggested that these agents may be effective in MDD, although limited sample size and lack of placebo control is a substantial problem.[57] A subsequent evidence-based review of 27 RCTs (of which 11 were placebo-controlled) found 5-HTP to be statistically superior in five trials.[58] The botanical *Rhodiola rosea*, was recently studied for AD efficacy using 340 versus 680 mg versus placebo for 6 weeks in mild-to-moderate depression and a significant reduction in mean depression ratings for both *Rhodiola rosea* groups was found, with no change with placebo.[59] Other CAM products showing AD-like activity include *Crocus sativus*, chromium piccolinate, *Lavandula augustifolia*, *Ginkgo biloba* and chamomile. An evidence-based review by Thachil and colleagues[60] identified two RCTs of *Crocus sativus*: a 6-week study versus fluoxetine (n = 40)[61] and a 6-week study versus imipramine (n = 30).[62] A placebo-controlled RCT of chamomile for generalized anxiety disorder (GAD) found a significantly greater reduction in the mean Hamilton Anxiety Rating score during chamomile versus placebo therapy, suggesting that chamomile may have modest anxiolytic activity in patients with mild-to-moderate GAD.[63]

Mind–Body Practices

Many individuals seeking CAM treatment for mood disorders may also turn to mind–body practices, such as meditation, yoga, qi-gong, tai-chi and acupuncture. Many of these practices rank among the top ten CAM practices reported by adults in the 2007 NHIS and use of meditation, yoga and deep-breathing exercises has increased significantly since the 2002 NHIS.[17]

Mindfulness-based Interventions

A report from the Agency for Healthcare Research and Quality, Department of Health and Human Services, reviewed the current state of research on a variety of meditation-based practices.[64] The report indicated that the overall data suggest therapeutic benefits from a variety of meditation-based practices for health conditions, including mood disorders. However, the data was ultimately insufficient to make any definitive conclusions about the usefulness of meditation in mood disorders. Mindfulness meditation, the core practice of Buddhist meditation, has been incorporated into several clinically-based meditation therapies, including mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT), the two most studied mindfulness interventions for mood disorders.[65] Mindfulness approaches are not considered to be relaxation or mood management techniques, but rather practices for cultivating greater self-awareness and acceptance. Practicing mindfulness has the potential to expand one's perspective, understanding and acceptance of oneself. Mindfulness training cultivates the ability to observe thoughts and feelings as events, similar to objects of sensory awareness, thereby cultivating the ability to respond reflectively rather than habitually or automatically.

Mindfulness-based stress reduction has been shown to have therapeutic benefits in several chronic illness populations, including those with mood disorders.[66] An early study of MBSR in 14 patients with anxiety found a reduction in blood pressure and decreases in depression, anxiety and general psychological distress in patients undergoing the MBSR therapy.[67] Meta-analyses have come to conflicting conclusions regarding MBSR's efficacy in patients with mood disorders. While one review of 15 studies on the effects of MBSR found no clear positive effects on depression symptoms in patients with comorbid medical disorders or in patients with mood disorders alone,[68] another systematic review and meta-analysis found mindfulness-based therapies to have robust within-group effect sizes in patients with anxiety and mood disorders that were maintained at follow-up.[69] A review of MBSR for chronic illnesses concluded that MBSR may help a broad range of individuals to cope with their clinical and nonclinical problems, including clinical depression, stress and anxiety.[70] Another meta-analysis of the effectiveness of MBSR on depression, anxiety and psychological distress across populations with different chronic somatic diseases found a reduction of anxiety and depression in patients undergoing MBSR therapy compared with wait-list controls.[71] Finally, a recent randomized wait-list control study of MBSR for patients with heterogeneous anxiety disorders found that, compared with controls, the MBSR group showed medium-to-large effect sizes on measures of anxiety and a large effect size for symptoms of depression, which were maintained at 6-month follow-up.[72]

The effectiveness of MBCT in chronic recurrent depression has been evaluated. One study comparing MBCT along with usual treatment in one group and only usual treatment in a control group found a decrease in reported symptoms in the MBCT group and no significant change in the usual-treatment group.[73] Another study found that patients who had MBCT training along with usual treatment had significantly fewer episodes of relapse/recurrence than those who did not have MBCT training.[74]

Yoga

A growing body of research suggests the efficacy of yoga in improving anxiety and depression. A review of five RCTs using different forms of yoga interventions in patients with a range of

disease severities showed overall positive findings, but methodological details, such as method of randomization, compliance with the yoga program and attrition rates, were not available.[75] One study of deep yoga relaxation found that it reduced depression among university students.[76] A pilot study of Vinyasa yoga (a style of yoga that includes flowing from one posture to another) as an adjunctive treatment for depressed patients who were not responding adequately to AD medication found that over a 2-month period, participants exhibited significant decreases in depression symptoms and significant increases in an aspect of mindfulness and in behavior activation.[77] Other studies also suggest the efficacy of yoga in the treatment of depression.[78–80] The decreased depression found in these yoga studies may relate to the changes in brain waves and the decreased cortisol levels reported during yoga postures and programs. One study with yoga instructors found that weekly yoga sessions led to increased α-waves and decreased cortisol.[81]

Yoga has also been shown to reduce anxiety. A wait-list control study of women with self-reported anxiety demonstrated that compared with controls, those in the yoga group showed decreased stress, anxiety, fatigue and depression, as well as increased well-being and vigor, after attending two weekly 90-min yoga sessions.[82] Yoga led to reductions of anxiety in women with breast cancer.[83] A systematic review of the effects of yoga on anxiety treatment identified five trials of individuals with clinically diagnosed anxiety disorders.[84] While the studies were small and methodologically flawed, the results were consistently positive. One trial showed substantial improvement in participants with obsessive–compulsive disorder[85] and another trial showed significant improvements in patients with mixed anxiety and depression.[86] It is possible that the potential underlying mechanisms for the positive effects of yoga on psychological and physiological conditions can include the stimulation of pressure receptors, leading to enhanced vagal activity and reduced cortisol.[87]

Acupuncture

Acupuncture originated as an aspect of the traditional Chinese medicine system. It is based upon the notion that the energy of one's life force, called Qi, runs throughout the body in a network of channels called meridians, which may be accessed at specific points on the skin. Disorders are conceived as alterations in the flow of Qi and the goal of acupuncture is to use needles to restore the balance of flow and equilibrium. Outcome studies have explored whether acupuncture works in a variety of psychological conditions, even though there is little understanding of its potential mechanism of action.

Although reviews of acupuncture do not arrive at uniform conclusions,[88] there is some evidence to suggest a potential role for this treatment modality. A recent meta-analysis of eight RCTs comparing 477 subjects showed that acupuncture could significantly reduce the severity of depression as measured by decreased scores of Hamilton Rating Scale for Depression (HAMD) or Beck Depression Inventory (BDI).[89] However, no significant effect of acupuncture was found on the response rate or remission rate. A review of seven trials involving 517 patients[90] included quantitative summaries of only one trial of 23 participants comparing acupuncture with sham acupuncture.[91] This analysis found a greater mean reduction in depression scores in patients receiving acupuncture. Results from five trials (409 participants), comparing acupuncture with medication, showed no difference in the reduction of depression, but the

findings were insufficient to determine the efficacy of acupuncture versus sham acupuncture. Another systematic review suggested that acupuncture was as effective as ADs.[92] A report of two randomized trials conducted in 20 patients experiencing symptoms of hypomania and a different set of 26 patients experiencing symptoms of depression associated with bipolar disease revealed that all patients experienced improvement over the course of study participation.[93] The acupuncture treatment appeared to target the symptom dimension of interest in both groups. Furthermore, the authors reported few negative side effects and good compliance with the acupuncture treatment. A recent analysis of 12 controlled trials of acupuncture in anxiety demonstrated generally positive findings.[94] Four of the RCTs focused on acupuncture in GAD or anxiety neurosis, while six focused on anxiety in the perioperative period. The review suggested that while more studies are needed, there were positive findings associated with acupuncture in the treatment of GAD or anxiety neurosis. It was also noted that there is limited evidence that favors the use of auricular acupuncture for perioperative anxiety.

One study in 30 patients scheduled to undergo colonoscopy, found that treatment with acupuncture decreased the patients' requests for sedating drugs, and thus reduced both discomfort and anxiety during the procedure.[95] Another randomized, blinded, controlled trial of ambulatory surgery patients reported significantly lower levels of anxiety in those treated with auricular acupuncture at relaxation points compared with controls.[96]

Expert Commentary

Many patients with depressive symptoms may not seek conventional treatment. Moreover, a recent review of conventional AD medications found that the benefit of these medications compared with placebo in patients with mild or moderate symptoms was minimal, although the benefit does increase with the severity of depression symptoms.[97] While questions remain regarding the methodological rigor of studies of CAM treatments for depression, the popularity of such interventions within the general Western population continues to grow. A few nutritional products, such as omega-3 fatty acids, as well as some key mind–body interventions, such as mindfulness meditation, may have a role in the overall treatment plan of patients with depressive mood disorders. Preliminary positive evidence of particular CAM remedies highlighted in this article suggests the need for further methodologically rigorous studies of CAM treatments.

Five-year View

There continues to be a greatly expanding body of research into the effects and mechanisms of CAM interventions for mood disorders. Studies will probably explore the physiological basis of CAM interventions on the brain and neurotransmitter systems with regard to mood disorders. More robust and methodologically sound RCTs will probably help to establish whether these interventions truly provide beneficial effects in certain patient populations. As this field of research develops over the next 5 years, it is likely that the data will provide a more detailed evaluation of CAM interventions, with more practical applications regarding potential beneficial effects, as well as helping to avoid adverse effects. Such data will provide both patients and healthcare providers with better information to carefully select CAM interventions that will be the most effective in managing mood disorders.

Sidebar

Key Issues

- It is important to study complementary and alternative medicine therapies for the treatment of mood disorders.
- Natural products may be effective in the management of mood disorders.
- Meditation-based practices help to improve levels of stress, depression and anxiety.
- Acupuncture may be useful in the treatment of mood disorders.
- The possible mechanism of action of different complementary and alternative medicine treatments for mood disorders is complex and not fully known.
- It is important to understand the potential negative effects of complementary and alternative medicine treatments when used for mood disorders.

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Papers of special note have been highlighted as:
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