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Complementary and alternative medicine therapies in mood disorders

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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.

KEYWORDS: acupuncture • anxiety • complementary and alternative medicine • depression • herbal supplements • meditation • mood disorders • supplements • yoga

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 monoamine 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, phenobarbital 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 monoamine neurotransmitters (dopamine, norepinephrine 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 there 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 angustifolia*, *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.

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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.

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest

- 1 Kessler RC, McGonagle KA, Zhao S *et al.* Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. *Arch. Gen. Psychiatry* 51, 8–19 (1994).
- 2 Simon G, Ormel J, von Korff M, Barlow W. Health care costs associated with depressive and anxiety disorders in primary care. *Am. J. Psychiatry* 152, 352–357 (1995).
- 3 Rice DP, Miller LS. Health economics and cost implications of anxiety and other mental disorders in the United States. *Br. J. Psychiatry* 34(Suppl.), 4–9 (1995).
- 4 Greenberg PE, Stiglin LE, Finkelstein SN, Berndt ER. The economic burden of depression in 1990. *J. Clin. Psychiatry* 54, 405–418 (1993).
- 5 Wang PS, Berglund P, Kessler RC. Recent care of common mental disorders in the United States, prevalence and conformance with evidence-based recommendations. *J. Gen. Intern. Med.* 15, 284–292 (2000).
- 6 The WHO World Mental Health Survey Consortium. Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. *JAMA* 291(21), 2581–2590 (2004).
- 7 Robins LN, Wing J, Wittchen H-U *et al.* The Composite International Diagnostic Interview, an epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Arch. Gen. Psychiatry* 45, 1069–1077 (1988).
- 8 WHO International Consortium in Psychiatric Epidemiology. Cross-national comparisons of the prevalences and correlates of mental disorders. *Bull. World Health Organ.* 78, 413–426 (2000).
- 9 Alegria M, Bijl RV, Lin E, Walters EE, Kessler RC. Income differences in persons seeking outpatient treatment for mental disorders, a comparison of the US with Ontario and The Netherlands. *Arch. Gen. Psychiatry* 57, 383–391 (2000).
- 10 Bijl RV, de Graaf R, Hiripi E *et al.* The prevalence of treated and untreated mental disorders in five countries. *Health Aff. (Millwood)* 22, 122–133 (2003).
- 11 Narrow WE, Rae DS, Robins LN, Regier DA. Revised prevalence estimates of mental disorders in the United States, using a clinical significance criterion to reconcile 2 surveys' estimates. *Arch. Gen. Psychiatry* 59, 115–123 (2002).
- 12 Wang PS, Lane M, Olfson M, Pincus HA, Wells KB, Kessler RC. Twelve-month use of mental health services in the United States, results from the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry* 62(6), 629–640 (2005).
- 13 Katz SJ, Kessler RC, Frank RG, Leaf PJ, Lin E. Mental health care use, morbidity, and socioeconomic status in the United States and Ontario. *Inquiry* 34, 38–49 (1997).
- 14 Kessler RC, Demler O, Frank RG *et al.* Prevalence and treatment of mental disorders, 1990–2003. *N. Engl. J. Med.* 352(24), 2515–2523 (2005).
- 15 Keyes KM, Hatzenbuehler ML, Alberti P, Narrow WE, Grant BF, Hasin DS. Service utilization differences for Axis I psychiatric and substance use disorders between white and black adults. *Psychiatr. Serv.* 59(8), 893–901 (2008).
- 16 Kessler RC, Greenberg PE, Mickelson KD, Meneades LM, Wang PS. The effects of chronic medical conditions on work loss and work cutback. *J. Occup. Environ. Med.* 43(Suppl. 3), 218–225 (2001).
- 17 Mao JJ, Farrar JT, Xie SX *et al.* Use of complementary and alternative medicine and prayer among a national sample of cancer survivors compared to other populations without cancer. *Complement. Ther. Med.* 15, 21–29 (2007).

- 18 Barnes PM, Bloom B, Nahin R. *Complementary and Alternative Medicine Use Among Adults and Children, United States, 2007*. National Health statistics reports; number 12. National Center for Health Statistics, MD, USA (2008).
- 19 Kessler RC, Soukup J, Davis RB *et al.* The use of complementary and alternative therapies to treat anxiety and depression in the United States. *Am. J. Psychiatry* 158(2), 289–294 (2001).
- 20 Freeman M, Mischoulon D, Tedeschini E *et al.* Complementary and alternative medicine for major depressive disorder, a meta-analysis of patient characteristics, placebo-response rates, and treatment outcomes relative to standard antidepressants. *J. Clin. Psychiatry* 71, 682–688 (2010).
- 21 Unutzer J, Klap R, Sturm R *et al.* Mental disorders and the use of alternative medicine, results from a national survey. *Am. J. Psychiatry* 157, 1851–1857 (2000).
- **National survey of almost 10,000 households assessing the use of complementary and alternative medicine therapies in people with mental health problems.**
- 22 Druss BG, Rosenheck RA. Use of practitioner-based complementary therapies by persons reporting mental conditions in the United States. *Arch. Gen. Psychiatry* 57, 708–714 (2000).
- 23 Simon GE, Cherkin DC, Sherman KJ *et al.* Mental health visits to complementary and alternative medicine providers. *Gen. Hosp. Psychiatry* 26, 171–177 (2004).
- 24 Wu P, Fuller C, Liu X *et al.* Use of complementary and alternative medicine among women with depression, results of a national survey. *Psychiatry Serv.* 58, 349–356 (2007).
- 25 Barner JC, Bohman TM, Brown CM, Richards KM. Use of complementary and alternative medicine for treatment among African-Americans, a multivariate analysis. *Res. Social Adm. Pharm.* 6, 196–208 (2010).
- 26 Pagan JA, Pauly MV. Access to conventional medical care and the use of complementary and alternative medicine. *Health Affairs* 24, 255–262 (2005).
- 27 Givens JL, Houston TK, van Voorhees BW *et al.* Ethnicity and preferences for depression treatment. *Gen. Hosp. Psychiatry* 29, 182–191 (2007).
- 28 Givens JL, Katz IR, Bellamy S *et al.* Stigma and the acceptability of depression treatments among African Americans and whites. *J. Gen. Intern. Med.* 22, 1292–1297 (2007).
- 29 Zollman C, Vickers A. What is complementary medicine? *BMJ* 319, 693–696 (1999).
- 30 Tindle HA, Davis RB, Phillips RS, Eisenberg DM. Trends in use of complementary and alternative medicine by US adults, 1997–2002. *Altern. Ther. Health Med.* 11, 42–49 (2005).
- 31 Greeson JM, Sanford B, Monti DA. St. John's wort (*Hypericum perforatum*), a review of the current pharmacological, toxicological, and clinical literature. *Psychopharmacology (Berl.)* 153(4), 402–414 (2001).
- 32 Field HL, Monti DA, Greeson JM, Kunkel EJ. St. John's Wort. *Int. J. Psychiatry Med.* 30(3), 203–219 (2000).
- 33 Linde K, Knuppel L. Large-scale observational studies of hypericum extracts in patients with depressive disorders – a systematic review. *Phytomedicine* 12, 148–157 (2005).
- **Systematic review of the effectiveness of hypericum (St John's wort) in the treatment of depression.**
- 34 Gastpar M, Singer A, Zeller K. Efficacy and tolerability of hypericum extract STW3 in long-term treatment with a once-daily dosage in comparison with sertraline. *Pharmacopsychiatry* 38, 78–86 (2005).
- 35 Kasper S, Angheliescu IG, Szegedi A, Dienel A, Kieser M. Superior efficacy of St John's wort extract WS 5570 compared to placebo in patients with major depression, a randomized, double-blind, placebo-controlled, multi-center trial. *BMC Med.* 4, 14 (2006).
- 36 Bjerkenstedt L, Edman GV, Alken RG, Mannel M. Hypericum extract LI 160 and fluoxetine in mild to moderate depression, a randomized, placebo-controlled multi-center study in outpatients. *Eur. Arch. Psychiatry Clin. Neurosci.* 255, 40–47 (2005).
- 37 Fava M, Alpert J, Nierenberg AA *et al.* A double-blind, randomized trial of St. John's wort, fluoxetine, and placebo in major depressive disorder. *J. Clin. Psychopharmacol.* 25, 441–447 (2005).
- 38 Moreno RA, Teng CT, Almeida KM, Tavares H. *Hypericum perforatum* versus fluoxetine in the treatment of mild to moderate depression, a randomized double-blind trial in a Brazilian sample. *Rev. Bras. Psiquiatr.* 28, 29–32 (2006).
- 39 Kaspar S, Gastpar M, Moller HJ, Muller We *et al.* Better tolerability of St. John's wort extract WS 5570 compared to treatment with SSRIs, a reanalysis of data from controlled trials in acute major depression. *Int. Clin. Psychopharmacol.* 25, 204–213 (2010).
- 40 Gurley BJ, Swain A, Williams DK, Barone G, Battu SK. Gauging the clinical significance of P-glycoprotein-mediated herb–drug interactions, comparative effects of St. John's wort, Echinacea, clarithromycin, and rifampin on digoxin pharmacokinetics. *Mol. Nutr. Food Res.* 52(7), 772–779 (2008).
- 41 Boyer EW, Shannon M. The serotonin syndrome. *N. Engl. J. Med.* 352 (11), 1112–1120 (2005).
- **Review and description of the serotonin syndrome, a potentially concerning side effect of some natural products used for mood disorders.**
- 42 Bottligliery T, Hyland K. S-adenosylmethionine levels in psychiatric and neurological disorders, a review. *Acta Neurol. Scand. Suppl.* 154, 12–26 (1994).
- 43 Mischoulon D, Fava M. Role of S-adenosyl-L-methionine in the treatment of depression, a review of the evidence. *Am. J. Clin. Nutr.* 76(Suppl.), S1158–S1161 (2002).
- 44 Echols JC, Naidoo U, Salzman C. SAME (S-adenosylmethionine). *Harv. Rev. Psychiatry* 8, 84–90 (2000).
- 45 Agency for Healthcare Research and Quality. *S-adenosyl-L-methionine (SAME) for Depression, Osteoarthritis, and Liver Disease*. Agency for Healthcare Research and Quality, MD, USA (2002).
- 46 Williams AL, Girard C, Jui D, Sabina A, Katz DL. S-adenosylmethionine (SAME) as treatment for depression, a systematic review. *Clin. Invest. Med.* 28, 132–139 (2005).
- **Systematic review of the use and effectiveness of S-adenosyl-methionine in patients with depression.**
- 47 Papakostas GI, Mischoulon D, Shyu I, Alpert JE, Fava M. S-adenosyl methionine (SAME) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder, a double-blind, randomized clinical trial. *Am. J. Psychiatry* 167(8), 942–948 (2010).
- 48 Janicak PG, Lipinski J, Davis JM, Altman E, Sharma RP. Parenteral S-adenosyl-methionine (SAME) in depression, literature review and preliminary data. *Psychopharmacol. Bull.* 25 (2), 238–242 (1989).

- 49 Haag M. Essential fatty acids and the brain. *Can. J. Psychiatry* 48, 195–203 (2003).
- 50 Stahl LA, Begg DP, Weisinger RS, Sinclair AJ. The role of omega-3 fatty acids in mood disorders. *Curr. Opin. Investig. Drugs* 9, 57–64 (2008).
- 51 Dyall SC, Michael-Titus AT. Neurological benefits of omega-3 fatty acids. *Neuromolecular Med.* 10, 219–235 (2008).
- 52 Williams AL, Katz D, Girard C, Goodman J, Bell I. Do essential fatty acids have a role in the treatment of depression? *J. Affect. Disord.* 93, 117–123 (2006).
- 53 Su KP, Huang SY, Chiu CC, Shen WW. Omega-3 fatty acids in major depressive disorder, a preliminary double-blind, placebo-controlled trial. *Eur. Neuropsychopharmacol.* 13, 267–271 (2003).
- 54 Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am. J. Psychiatry* 159, 477–479 (2002).
- 55 Freeman MP, Hibbeln JR, Wisner KL *et al.* Omega-3 fatty acids, evidence basis for treatment and future research in psychiatry. *J. Clin. Psychiatry* 67, 1954–1967 (2006).
- 56 Parker G, Gibson NA, Brotchie H *et al.* Omega-3 fatty acids and mood disorders. *Am. J. Psychiatry* 163, 969–978 (2006).
- 57 Shaw K, Turner J, Del Mar C. Tryptophan and 5-hydroxytryptophan for depression. *Cochrane Database Syst. Rev.* 1, CD003198 (2002).
- 58 Turner EH, Loftis JM, Blackwell AD. Serotonin *a la carte*, supplementation with the serotonin precursor 5-hydroxytryptophan. *Pharmacol. Ther.* 109, 325–338 (2006).
- 59 Darbinyan V, Aslanyan G, Amroyan E, Gabrielyan E, Malstrom C, Panossian A. Clinical trial of *Rhodiola rosea* L. extract SHR-5 in the treatment of mild to moderate depression. *Nord. J. Psychiatry* 61, 343–348 (2007).
- **Clinical trial demonstrating the potential effectiveness of *Rhodiola rosea* for the treatment of depression.**
- 60 Thachil AF, Mohan R, Bhugra D. The evidence base of complementary and alternative therapies in depression. *J. Affective Dis.* 97, 23–35 (2007).
- 61 Noorbala S, Akhondzadeh N, Tahmacebi-Pour N, Jamshidi AH. Hydro-alcoholic extract of *Crocus sativus* L. versus fluoxetine in the treatment of mild to moderate depression, a double-blind, randomized pilot trial. *J. Ethnopharmacol.* 97 (2), 281–284 (2005).
- 62 Akhondzadeh L, Kashani A, Fotouhi S *et al.* Comparison of *Lavandula angustifolia* Mill. Tincture and imipramine in the treatment of mild to moderate depression, a double-blind, randomized trial. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 27 (1), 123–127 (2003).
- 63 Amsterdam J, Li Y, Soeller I *et al.* A randomized, double-blind, placebo-controlled trial of oral *matricaria recutita* (chamomile) extract therapy for generalized anxiety disorder. *J. Clin. Psychopharmacol.* 29, 378–382 (2009).
- 64 Ospina MB, Bond TK, Karkhaneh M *et al.* *Meditation Practices for Health, State of the Research.* Evidence Report/Technology Assessment No. 155. Agency for Healthcare Research and Quality, MD, USA (2007).
- 65 Bishop SR, Lau M, Shapiro S *et al.* Mindfulness, a proposed operational definition. *Clin. Psychol. Sci. Pract.* 11(3), 230–241 (2004).
- 66 Grossman P, Niemann L, Schmidt S *et al.* Mindfulness-based stress reduction and health benefits, a meta-analysis. *J. Psychosom. Res.* 57(1), 35–43 (2004).
- 67 Zinn JK, Massion AO, Kristeller J. Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. *Am. J. Psychiatry* 149, 936–943 (1992).
- **One of the original clinical studies of mindfulness meditation for mental health problems.**
- 68 Toneatto T, Nguyen L. Does mindfulness meditation improve anxiety and mood symptoms? A review of the controlled research. *Can. J. Psychiatry* 52(4), 260–266 (2007).
- 69 Hofmann SG, Sawyer AT, Witt AA, Oh D. The effect of mindfulness-based therapy on anxiety and depression, a meta-analytic review. *J. Consult. Clin. Psychology* 78, 169–183 (2010).
- 70 Niazi AK, Niazi SK. Mindfulness-based stress reduction, a non-pharmacological approach for chronic illness. *North Am. J. Med. Sci.* 3, 20–23 (2010).
- 71 Bohlmeijer E, Prenger R, Taal E. The effects of mindfulness-based stress reduction therapy on mental health of adults with a chronic medical disease, a meta-analysis. *J. Psychosom. Res.* 68(6), 539–544 (2010).
- 72 Vollestad J, Sivertsen B, Nielsen GH. Mindfulness-based stress reduction for patients with anxiety disorders, Evaluation in a randomized controlled trial. *Behav. Res. Ther.* 49, 281–288 (2011).
- 73 Barnhofer T, Crane C, Hargus E. Mindfulness-based cognitive therapy as a treatment for chronic depression, a preliminary study. *Behav. Res. Ther.* 47, 366–373 (2009).
- 74 Teasdale JD, Segal ZV, Williams JM. Prevention of relapse/recurrence in major depression by mindfulness-based cognitive therapy. *J. Consult. Clin. Psychol.* 68, 615–623 (2000).
- 75 Pilkington K, Kirkwood G, Rampes H, Richardson J. Yoga for depression, the research evidence. *J. Affect. Disord.* 89, 13–24 (2005).
- 76 Khumar SS, Kaur P, Kaur S. Effectiveness of Shavasana on depression among university students. *Indian J. Clin. Psychol.* 20, 82–87 (1993).
- 77 Uebelacker LA, Tremont G, Epstein-Lubow G *et al.* Open trial of Vinyasa yoga for persistently depressed individuals, evidence of feasibility and acceptability. *Behav. Modif.* 34(3), 247–264 (2010).
- 78 Butler LD, Waelde LC, Hastings TA *et al.* Meditation with yoga, group therapy with hypnosis, and psychoeducation for long-term depressed mood, a randomized pilot trial. *J. Clin. Psychol.* 64(7), 806–820 (2008).
- 79 Janakiramaiah N, Gangadhar BN, Naga Venkatesha Murthy PJ, Harish MG, Subbakrishna DK, Vedamurthachar A. Antidepressant efficacy of Sudarshan Kriya Yoga (SKY) in melancholia, a randomized comparison with electroconvulsive therapy (ECT) and imipramine. *J. Affect. Disord.* 57 (1–3), 255–259 (2000).
- 80 Woolery A, Myers H, Sternlieb B, Zeltzer L. A yoga intervention for young adults with elevated symptoms of depression. *Altern. Ther. Health Med.* 10(2), 60–63 (2004).
- 81 Kamei T, Toriumi Y, Kimura H, Ohno S, Kumano H, Kimura K. Decrease in serum cortisol during yoga exercise is correlated with α wave activation. *Percept. Mot. Skills* 90(3 Pt 1), 1027–1032 (2000).
- 82 Michalsen A, Grossman P, Acil A *et al.* Rapid stress reduction and anxiolysis among distressed women as a consequence of a three-month intensive yoga programme. *Med. Sci. Mon.* 11(12), 555–561 (2005).
- 83 Rao MR, Raghuram N, Nagendra HR *et al.* Anxiolytic effects of a yoga program in early breast cancer patients undergoing conventional treatment. A randomized controlled trial. *Complement. Ther. Med.* 17, 1–8 (2009).

- 84 Kirkwood G, Rampes H, Tuffrey V, Richardson J, Pilkington K. Yoga for anxiety, a systematic review of the research evidence. *Br. J. Sports Med.* 39(12), 884–891 (2005).
- 85 Shannahoff-Khalsa DS, Ray LE, Levine S, Gallen CC, Schwartz BJ, Sidorowich JJ. Randomized controlled trial of yogic meditation techniques for patients with obsessive-compulsive disorder. *CNS Spectr.* 4(12), 34–47 (1999).
- 86 Gupta N, Khera S, Vempati RP, Sharma R, Bijlani RL. Effect of yoga based lifestyle intervention on state and trait anxiety. *Indian J. Physiol. Pharmacol.* 50(1), 41–47 (2006).
- 87 Field T. Yoga clinical research review. *Complement. Ther. Clin. Pract.* 17(1), 1–8 (2010).
- 88 Ernst E, Lee MS, Choi TY. Acupuncture for depression? A systematic review of systematic reviews. *Eval. Health Prof.* DOI: 10.1177/0163278710386109 (2011) (Epub ahead of print).
- 89 Wang H, Qi H, Wang BS, Cui YY, Zhu L, Rong ZX, Chen HZ. Is acupuncture beneficial in depression, a meta-analysis of 8 randomized controlled trials? *J. Affect. Disord.* 111(2–3), 125–134.
- **Meta-analysis of the effectiveness of acupuncture in patients with depression.**
- 90 Smith CA, Hay PPJ. Acupuncture for depression. *Cochrane Database Syst. Rev.* 18, CD004046 (2005).
- 91 Allen JJB, Schnyer RN, Hit SK. The efficacy of acupuncture in the treatment of major depression in women. *Psychol. Sci.* 9, 397–401 (1998).
- 92 Leo RJ, Ligo JS. A systematic review of randomized controlled trials of acupuncture in the treatment of depression. *J. Affect. Disord.* 97, 13–22 (2007).
- 93 Dennehy EB, Schnyer R, Bernstein IH *et al.* The safety, acceptability, and effectiveness of acupuncture as an adjunctive treatment for acute symptoms in bipolar disorder. *J. Clin. Psychiatry* 70(6), 897–905 (2009).
- 94 Pilkington K, Kirkwood G, Rampes H, Cummings M, Richardson J. Acupuncture for anxiety and anxiety disorders – a systematic literature review. *Acupunct. Med.* 25(1–2), 1–10 (2007).
- 95 Fanti L, Gemma M, Passaretti S *et al.* Electroacupuncture analgesia for colonoscopy. A prospective, randomized, placebo-controlled study. *Am. J. Gastroenterol.* 98, 312–316 (2003).
- 96 Wu S, Liang J, Shu X, Liu X, Miao D. Comparing the treatment effectiveness of body acupuncture and auricular acupuncture in preoperative anxiety treatment. *J. Res. Med. Sci.* 16, 39–42 (2011).
- 97 Fournier JC, DeRubeis RJ, Hollon SD *et al.* Antidepressant drug effects and depression severity, a patient-level meta-analysis. *J. Am. Med. Assoc.* 303(1), 47–53 (2010).