

Review

Complementary and alternative medicine in the treatment of bipolar disorder — A review of the evidence [☆]

Carmen Andreescu ^{a,b}, Benoit H. Mulsant ^{a,c,*}, James E. Emanuel ^a

^a *The Advanced Center for Interventions and Services Research for Late-life Mood Disorders, Department of Psychiatry, University of Pittsburgh School of Medicine, United States*

^b *John A. Hartford Center of Excellence in Geriatric Psychiatry, Pittsburgh, United States*

^c *Centre for Addiction and Mental Health and Department of Psychiatry, University of Toronto, Canada*

Received 29 September 2007; received in revised form 20 March 2008; accepted 26 March 2008

Available online 5 May 2008

Abstract

A growing number of patients with mood disorders are using complementary and alternative medicine (CAM) interventions. In this paper, we review the published scientific evidence on the benefits and risks of CAM for the treatment of patients with bipolar disorder. Since very few studies of CAM have involved patients with bipolar disorder, most available evidence is derived from trials conducted in patients with major depressive disorder. The use of omega-3 fatty acids has been studied in two controlled studies in bipolar disorder while St. John's wort (*Hypericum perforatum*), S-adenosyl-L-methionine (SAME), and acupuncture have been studied in a series of randomized controlled trials in patients with major depression. Overall, the best evidence supports the use of St. John's wort for the treatment of mild to moderate depression. SAME may also be effective for depression. However, both of these products have the potential to induce mania; the extent of this risk needs to be quantified. St. John's wort can also interact with a variety of medications. Evidence regarding the benefits of omega-3 fatty acids or acupuncture is inconsistent. Data regarding other CAM interventions (e.g., aromatherapy massage, massage therapy, yoga) are almost entirely lacking. In conclusion, better studies are needed before CAM interventions can be recommended to patients with bipolar disorder. In the meantime, patients need to be informed about the possible risks associated with the use of these interventions.

© 2008 Elsevier B.V. All rights reserved.

Keywords: Complementary medicine; Alternative medicine; Bipolar disorder; Bipolar depression; Omega-3 fatty acids; Hypericum; SAME; Kava-kava; Acupuncture; Therapeutic massage; Yoga; Herbal remedies

Contents

1. Introduction	17
2. Omega-3 fatty acids.	18

[☆] Supported in part by PHS grants AT001218, MH 069430, MH 071944 and MH068846.

* Corresponding author. Geriatric Mental Health Program, CAMH, 1001 Queen Street West, Toronto, Ontario, Canada M6J 1H4. Tel.: +1 416 535 8501x4749; fax: +1 416 583 1307.

E-mail address: benoit_mulsant@camh.net (B.H. Mulsant).

3. St. John's wort (<i>Hypericum perforatum</i>)	19
4. Other herbal products	20
5. S-adenosyl-L-methionine (SAMe)	21
6. Acupuncture	22
7. Other CAM modalities: aromatherapy massage, therapeutic massage, yoga	22
8. Other potential uses of CAM by patients with bipolar disorder	23
9. Conclusion	23
Role of the funding source	23
Conflict of interest.	23
Acknowledgements	23
References	24

1. Introduction

Bipolar disorder is associated with a markedly lower quality of life, functional impairment, disability, and premature death due to suicide or comorbid physical illness (Murray and Lopez, 1997; Morgan et al., 2005). Despite the availability of several pharmacological treatments, many Americans who suffer from bipolar disorder have only a partial response, experience adverse effects, or refuse to take conventional treatments (Fleck et al., 2005). A growing number of these patients are using complementary and alternative medicine (CAM) therapies, following a trend observed in Americans with a variety of medical disorders (Ernst, 2003). CAM therapies are defined by the National Center for Complementary and Alternative Medicine as a group of diverse medical and health systems, practices, and products that are not currently considered to be part of conventional medicine (National Center for Complementary and Alternative Medicine — National Institutes of Health, 2002). A national US survey noted a 47% increase in total visits to CAM practitioners, from 427 million in 1990 to 629 million in 1997, exceeding total visits to primary care physicians (Eisenberg et al., 1998). Estimated expenditures for CAM professional services were conservatively estimated at \$21.2 billion in 1997, with at least \$12.2 billion of out-of-pocket expenditures, exceeding out-of-pocket expenditures for all US hospitalizations (National Center for Complementary and Alternative Medicine — National Institutes of Health, 2002). In this survey, alternative medicine use and expenditures were primarily attributed to an increase in the proportion of the population seeking CAM therapies, rather than an increase number of visits per patient (Eisenberg et al., 1998). In a more recent nationwide survey, 36% of US adults aged 18 years and over use some form of CAM (Barnes et al., 2004).

Use of CAM therapies is apparently not driven by dissatisfaction with conventional medicine. Rather, it has been associated with higher level of education, poorer health status, environmentalism, feminism, and interest in spirituality and personal growth psychology (Astin, 1998). In a large mail survey (Gray et al., 2002), 42% of the patients in a managed care organization reported using at least one CAM therapy, most commonly relaxation techniques (18%), massage (12%), herbal medicine (10%), or megavitamin therapy (9%). Perceived efficacy of CAM was very high, ranging from 98% (energy healing) to 76% (hypnosis). CAM users tended to be female, younger, better educated, and employed (Gray et al., 2002).

A 2001 US survey of a nationally representative sample of patients diagnosed with a mood or anxiety disorder reported that 57% of those with anxiety attacks and 54% of those with severe depression were using CAM therapies to treat these conditions (either as primary or as adjunctive medication) (Kessler et al., 2001). These proportions increased to 66%–67% respectively among those who were seeing a conventional health care professional for these conditions (Kessler et al., 2001). The perceived helpfulness of CAM therapies was similar to that of conventional therapies (Kessler et al., 2001).

While there are several reviews in the literature regarding the use of CAM in unipolar depression, to our knowledge there is no review regarding the use of CAM in bipolar illness. Given CAM's widespread and growing popularity and given some of the particularities of patients with bipolar illness (increased novelty seeking during manic/hypomania phases), it is likely that a large number of persons with bipolar disorders are using CAM to treat their symptoms or to remedy the adverse effects of their conventional treatment. Mental health professionals who provide care to these patients need to be knowledgeable about the available data on

the efficacy and safety of CAM for the treatment of symptoms associated with bipolar disorder. This paper presents a review of data published in the English literature over the past 10 years, with a focus on CAM therapies for which controlled data are available (see Table 1).

To identify articles, we conducted a systematic search of the MEDLINE database and of the Cochrane Database of Systematic Reviews for English articles published between January 1996 and September 2006 using the following keywords: “bipolar disorder”, “bipolar depression”, “complementary medicine”, “omega-3 fatty acids”, “hypericum”, “SAME”, “acupuncture”, “kava-kava”, “therapeutic massage”, “yoga” and “herbal remedies”. We also performed a manual search of the reference lists of relevant retrieved articles. Because of their potential relevance to bipolar disorder, we also reviewed some papers identified in our systematic search that addressed the treatment of depressive (given the potential risk of manic switch for substances with possible antidepressant effect) or other psychiatric disorders. However, we did not perform a systematic search of CAM treatments for unipolar major depression or psychiatric disorders other than bipolar disorder. Also, we did not review the evidence related to light therapy, given that it is usually considered a mainstream treatment and the documented risk of mania (Kripke, 1998) which limits its use in bipolar disorder.

2. Omega-3 fatty acids

Following the well-publicized promising results from a placebo-controlled study (Stoll et al., 1999), there has been a broad interest in the use of omega-3 fatty acids

for the treatment of bipolar disorder. Omega-3 fatty acids are found principally in fish and seafood although some can be derived from green vegetables. By contrast, omega-6 fatty acids are found in soft margarine, most vegetable oils, and animal fat. Omega-6 are plentiful in most modern western diets while omega-3 are often relatively lacking. A high dietary ratio of omega-6 to omega-3 has been linked to vulnerability to many physical and mental disorders (Simopoulos, 2003). There is mounting evidence that dietary supplementation with omega-3 fatty acids may be beneficial in a variety of conditions including several psychiatric disorders (Freeman, 2000; Tanskanen et al., 2001), although not all studies are in agreement (Hakkarainen et al., 2004). This evidence comprises randomized controlled trials in patients with depression, bipolar disorder, schizophrenia, and borderline personality disorder (Stoll et al., 1999; Nemets et al., 2002; Peet and Horrobin, 2002b; Zanarini and Frankenburg, 2003).

Epidemiological data suggest that rates of bipolar disorder in various countries are negatively associated with the consumption of fish and seafood (Hibbeln, 2002). Omega-3 fatty acids may modulate neurotransmitter metabolism and it has been proposed that they inhibit neuronal signal transduction in a manner similar to that of lithium and valproate, two effective treatments for bipolar disorder (Osher et al., 2005). Also, in an MRI study, patients with bipolar disorder who received omega-3 fatty acids experienced a significant dose-dependent decrease in their brain-water proton transverse (T2) relaxation times. This finding is consistent with the hypothesis that omega-3 fatty acids alter neuronal membrane fluidity (Hirashima et al., 2004). A recent randomized placebo-controlled study assessed the effect of treatment with eicosapentaenoic acid (EPA;

Table 1
Complementary and alternative medicine interventions for the treatment of symptoms associated with bipolar disorder studied under controlled conditions

Mode of intervention	Therapeutic target in bipolar disorder	Scientific evidence		Main risks and adverse effects
		Depression	Bipolar disorder	
Acupuncture	Depressive phase of illness	8 controlled trials	None	Minimal
Omega-3 fatty acids	Mood stabilization Depressive phase of illness	Several RCTs	Several open trials; two RCTs	Fishy aftertaste; gastrointestinal distress
St. John's wort	Depressive phase of illness	Close to 40 RCTs	None	Mania; serotonergic syndrome; photosensitivity
SAMe	Depressive phase of illness	Several RCTs	None	Mania; gastrointestinal distress; headache

SAMe: S-adenosyl-L-methionine; RCT: randomized controlled trial.

one of the omega-3 fatty acids) on brain levels of *N*-acetyl-aspartate (NAA) with magnetic resonance spectroscopy (Frangou et al., 2006b). A significant increase in NAA levels was observed in bipolar patients treated with EPA (2 g/day for 12 weeks) when compared to the placebo group. Based on these results, the authors hypothesized that EPA has a neurotrophic role in the treatment of bipolar disorder (Frangou et al., 2006b).

Open studies have reported an improvement of bipolar depression with omega-3 fatty acids (Osher et al., 2005) and it has been suggested that omega-3 fatty acids may be more beneficial in the depressive than in the manic phase of bipolar disorder (Chiu et al., 2005). In a widely publicized 4-month study, supplementation of usual treatment with either omega-3 fatty acids (9.6 g/day) or olive oil (placebo) were compared under double-blind randomized condition in 30 patients with bipolar disorder (Stoll et al., 1999). The patients who received omega-3 fatty acids had a significantly longer period of remission than those in the placebo group. Omega-3 fatty acids outperformed placebo for nearly every outcome measure that was assessed. The authors concluded that omega-3 fatty acids were well tolerated and improved the short-term course of illness in patients with bipolar disorder (Stoll et al., 1999). In a critique of this study, Calabrese et al. (1999) emphasized several limitations: (1) patients enrolled in this study were either mildly ill or not at all acutely ill at the time of study entry; (2) although the design was described as following an intent-to-treat principle, several patients were excluded from the analysis after they began treatment; and (3) changes in the Young Mania Rating Scale experienced by the omega-3 fatty acids and placebo groups did not differ significantly (even though there were significant differences on the Clinical Global Impression [CGI] scale, the Global Assessment Scale, and the Hamilton Rating Scale for Depression [Ham-D]). Two randomized, double-blind, placebo-controlled trials on the adjunctive efficacy of EPA in the treatment of bipolar depression have been published in 2006. The two trials have conflicting results. Frangou et al. (2006a) reported on a 12-week study showing EPA (1 g/day, $N=24$ or 2 g/day, $N=25$) to be associated with a significant improvement in both Ham-D and CGI scores compared to placebo. In another 4-month trial of EPA (6 g/day, $N=116$) in the treatment of bipolar depression and rapid cycling bipolar disorder, Keck et al. (2006) did not find any significant difference between EPA and placebo. Since several placebo-controlled studies have reported positive results when lower doses of EPA (1–2 g/day) were added to conventional antidepressants in patients with major depressive disorder (MDD)

(Nemets et al., 2002; Peet and Horrobin, 2002a; Marangell et al., 2003), it is possible that 6 g/day of EPA is too high a dose for effective treatment of bipolar depression. However, other recent placebo-controlled trials in MDD have used higher doses of EPA (Su et al., 2003). Alternatively, other factors pertaining to change in levels of omega-3 fatty acids in different subgroups may explain these inconsistent results (Post et al., 2003). A recent meta-analysis of placebo-controlled trials (Lin and Su, 2007) reported significant antidepressant efficacy of omega-3 fatty acids, but concluded that a definitive validation of this finding warrants further larger and better controlled trials.

Omega-3 fatty acids have been reported to be safe and well tolerated: minor side effects (e.g., fishy aftertaste, gastrointestinal disturbances) seem to be dose dependent. Also, omega-3 fatty acids exert a dose-related effect on bleeding time. However, there are no documented cases of abnormal bleeding as a result of fish oil supplementation, even at high dosages and in combination with other anticoagulant medications (Eritsland et al., 1996). One study has looked at the concentration in fish oil supplements of several toxins that are known to accumulate in fish (i.e., mercury, polychlorinated biphenyls, and organochlorine pesticides) (Melanson et al., 2005). The results of this study suggest that fish oil supplements are more healthful than fish and that purified supplements may provide the benefits of omega-3 fatty acids without the risk of toxicity associated with the consumption of fish (Melanson et al., 2005).

In summary, omega-3 fatty acids may have a role in the treatment of bipolar disorder. However, given the conflicting data on their efficacy, additional studies are needed before their use can be recommended confidently to patients. These studies should clarify the role and the optimal dose of omega-3 fatty acids or EPA in the treatment of the depressive or manic phase of bipolar disorder and address lingering questions regarding the purity of marketed supplements.

3. St. John's wort (*Hypericum perforatum*)

Of CAM therapies potentially used in the treatment of symptoms associated with bipolar disorder, extracts from St. John's wort (SJW), *H. perforatum*, have probably been the most rigorously studied. These extracts have long been promoted by herbalists for the treatment of depression and are approved in Germany for this indication. Their use has been widely publicized and they have been touted for their safety and tolerability compared with antidepressant medications

regulated by the FDA (Moses and Mallinger, 2000). The mechanism of action of SJW has not been established. Hyperforin and hypericin, two components of SJW, inhibit serotonin, norepinephrine, and dopamine synaptic uptake (Guzelcan et al., 2001). The main *in vitro* effects of hyperforin (at concentrations of 0.1–1 μM) are non-specific presynaptic effects, resulting in the non-selective inhibition of the uptake of many neurotransmitters, and an interaction with dopamine D1 and opioid receptors (Mennini and Gobbi, 2004).

A meta-analysis of 37 double-blind randomized controlled trials that have compared clinical effects of SJW with either placebo or a standard antidepressant in adults with depressive disorders concluded that the evidence is inconsistent and confusing although SJW might be beneficial for mild to moderate depressive symptoms (Linde et al., 2005). While some placebo-controlled trials in patients who meet criteria for major depression suggest that SJW has minimal beneficial effects, other trials suggest benefits comparable to conventional antidepressants (Linde et al., 2005). This confusion is illustrated by another recent double-blind randomized trial comparing SJW, fluoxetine, and placebo in 135 patients with major depressive disorder. In this trial, SJW was significantly more efficacious than fluoxetine but did not differ significantly from placebo (Fava et al., 2005).

Several case reports have described SJW-induced mania in patients with unipolar depression or bipolar (I or II) disorder (Nierenberg et al., 1999; Moses and Mallinger, 2000; Fahmi et al., 2002). The older ages of the reported cases suggest that patients over 50 years may have a greater susceptibility to SJW-induced mania. Possible explanations include age-associated decrease in drug metabolism or increase in central nervous system drug sensitivity (Moses and Mallinger, 2000). Also, there are multiple reports of clinically significant drug interactions between SJW and a variety of drugs. SJW lowers the plasma concentration (or the pharmacological effect) of a number of drugs including alprazolam, amitriptyline, cyclosporine, digoxin, fexofenadine, indinavir, irinotecan, methadone, nevirapine, simvastatin, tacrolimus, theophylline, warfarin, and oral contraceptives (Izzo, 2004). The induction by SJW of P-glycoprotein or cytochrome P450 (CYP) enzymes (particularly CYP 3A4 and CYP 1A2) explains these pharmacokinetic interactions (Izzo, 2004; Shibayama et al., 2004). With the increased accessibility and use of SJW in the US, other adverse effects that are less common have also been reported, including photosensitivity and serotonin syndrome when SJW is combined with serotonin reuptake inhibitor antidepressants (e.g.,

paroxetine or sertraline), nefazodone, or buspirone (Izzo, 2004). Also, it is worth noting that there is considerable variation in the content and stability of SJW commercial products: a study that found a 189-fold difference in hyperforin content across eight commercial products (los Reyes and Koda, 2002).

Based on the available data, SJW can be recommended for the treatment of mild or moderate depression to patients with bipolar disorder who do not tolerate conventional antidepressants. These patients need to be warned that SJW may be better tolerated but it is not necessarily safer than these antidepressants (Moses and Mallinger, 2000). Patients with bipolar disorder need to be monitored for a possible switch to mania (in particular if they are older). The addition of a mood stabilizer might decrease this risk but clinicians need to be aware of potentially problematic interactions with other drugs (in particular loss of efficacy of oral contraceptives in their patients who are treated with teratogenic mood stabilizers).

4. Other herbal products

Many users of CAM may take a variety of herbal products other than SJW. In primary care settings, 11% of patients with symptoms of anxiety or depression reported using herbal products. Their use was predicted by a diagnosis of major depression, higher education, and a lower burden of medical illness (Roy-Byrne et al., 2005). Various herbal products (e.g., corni fructus, lycii fructus, pinelliae rhizome, or rehmanniae radix preparat) are used in treatment of depression in different parts of the world even though most of them have not been scientifically evaluated (Kang et al., 2005). One product has been evaluated in persons with bipolar disorder (Zhang et al., 2005) and three in rodent models of depression (Kaneko et al., 2005; Kang et al., 2005; Ito et al., 2006).

Free and Easy Wanderer Plus (FEWP) has been assessed in a 12-week randomized, placebo-controlled trial, in which the efficacy and safety of carbamazepine (CBZ) alone, CBZ plus FEWP, or placebo were compared in 124 patients with bipolar depression and 111 with mania (Zhang et al., 2005). The exact nature of FEWP is uncertain. The authors described it as containing eleven different herbal materials obtained from a local company of herbal supplies (Zhang et al., 2005). CBZ monotherapy produced significantly greater improvement than placebo in both manic and depressive symptoms. CBZ plus FEWP produced significantly greater improvement than CBZ monotherapy in depressive but not in manic symptoms. The study was

extended to 26 weeks and a follow-up report (Zhang et al., 2007) examined drop out rates and reported on an additional study of monotherapy with FEWP. In the study extension, drop out rates, side effects, and serum CBZ levels were lower for the CBZ plus FEWP than the CBZ plus placebo groups. FEWP monotherapy was reported to have a higher clinical response (defined as >50% response as measured by the Hamilton Rating Scale for Depression or the Young Mania Rating Scale) in a significantly higher percent of subjects than placebo (74.4% vs. 41.7%). These results, suggesting that FEWP may have beneficial effects in depressed bipolar patients, need to be replicated.

Koso-san (xiang-su-san in Chinese) is used in East Asia for the treatment of the common cold, food-induced allergic urticaria, irritable bowel syndrome, chronic fatigue syndrome, insomnia, other depressive symptoms, and “autonomic imbalance.” In one study mice were subjected to a combination of forced swimming and chronic mild stresses that were considered to constitute an animal model of depression. Koso-san significantly shortened the duration of immobility and suppressed the HPA axis hyperactivity in these “depressed” mice (Ito et al., 2006). However, to our knowledge, there is no published evaluation of the antidepressant activity of koso-san in humans. Similarly, two other herbal products, hange-koboku-to and nelumbinis semen, have been reported to have antidepressant properties in rats or mice (Kaneko et al., 2005; Kang et al., 2005) but they have not been properly evaluated in humans. The exact mechanism of action of any of these herbal supplements is not known. Recent data suggest that Koso-san’s antidepressant qualities are related to suppressing the hyperactivity of the HPA axis in rodent models (Ito et al., 2006).

Kava-kava (piper methysticum *G. forster*) has been used by Pacific islanders in social and ceremonial events since ancient times due to its psychotropic effects. Several extracts of its biologically active constituents (kavalactones) are being marketed as herbal products for anxiety disorders or as dietary supplements to improve stress, nervous tension, and restlessness (Bilia et al., 2002). Several recent double-blind studies of its efficacy in anxiety disorders have had negative results (Jacobs et al., 2005; Connor et al., 2006). However, an earlier meta-analysis supported its efficacy in the treatment of anxiety disorders (Pittler and Ernst, 2003). So far, there have been no controlled studies of kava-kava in patients with bipolar disorder. Despite the absence of toxicity observed in controlled studies (Connor et al., 2006), case reports of serious hepatotoxicity (including cases of liver failure) associated with kavalactones preparations

have led to their ban in several countries and patients should be cautioned about this potentially lethal side effect (Escher et al., 2001; Wheatley, 2005). Several studies investigated the mechanism of action of piper methysticum – especially in anxiety – and in vitro studies suggest that kavapyrones (the pharmacologically active components) mediate the effect of GABA-A receptors in the hippocampus and the amygdala (Jussofie et al., 1994).

Cannabis (marijuana) was reported to benefit some patients with bipolar disorder in a case series (Grinspoon and Bakalar, 1998). However, the authors concluded that the potential of cannabis as a treatment for bipolar disorder cannot be assessed in the present social circumstances (Grinspoon and Bakalar, 1998).

In summary, at the present time, given the lack of data on the efficacy of herbal products other than SJW in the treatment of bipolar disorder and their potential for unrecognized adverse effects, clinicians cannot safely recommend the use of these products and need to warn their patients that “natural” does not mean safe (c.f., Socrates’ hemlock).

5. S-adenosyl-L-methionine (SAME)

Together with SJW (see above), S-adenosyl-L-methionine (SAME) is one of the CAM products that has been studied under rigorous controlled conditions. SAME is derived from the amino acid L-methionine through the one-carbon cycle and it is a methyl donor involved in the synthesis of the monoaminergic neurotransmitters. SAME has been investigated for its antidepressant properties in both open (Lipinski et al., 1984) and randomized controlled trials (Mischoulon and Fava, 2002). SAME dosages of 200–1600 mg/day (orally or parenterally) have been shown to be superior to placebo and as effective as tricyclic antidepressants in alleviating depression, although some individuals may require higher doses (Lipinski et al., 1984; Mischoulon and Fava, 2002). SAME may have a faster onset of action than conventional antidepressants and may potentiate the effect of tricyclic antidepressants (Mischoulon and Fava, 2002) or of serotonin reuptake inhibitors (Alpert et al., 2004). Oral dosages of SAME up to 1600 mg/day appear to be significantly bioavailable and safe (Goren et al., 2004). SAME has been associated with minor adverse effects, e.g., gastrointestinal symptoms and headaches (Alpert et al., 2004). However, as with any antidepressant compound, some cases of mania have been reported in bipolar patients taking SAME (Carney et al., 1989; Mischoulon and Fava, 2002).

Overall, SAME appears to be safe and efficacious in the treatment of depression but further controlled studies are indicated as current evidence comes mostly from open trials or small controlled studies. It may have a role in the management of patients with bipolar disorder but more research is needed, in particular to determine its effective dose and to better assess the risk of switch to mania or hypomania (Mischoulon and Fava, 2002).

6. Acupuncture

Acupuncture and electroacupuncture popularity is increasing in the Western world for the treatment of a variety of conditions, including anxiety and depression (Eisenberg et al., 1998; Ernst et al., 1998; Kessler et al., 2001). The World Health Organization reports that there are approximately 10,000 trained acupuncturists in the US, including 3000 physicians. The exact mechanisms of action of acupuncture are unknown. One hypothesis supported by animal data is that acupuncture influences norepinephrine metabolism in the brain (Luo et al., 1998).

Early published abstracts from China and the former Soviet Union suggested that acupuncture might be of benefit in the treatment of mood disorders (Han, 1986; Polyakov, 1988; Hu, 1996; Mischoulon and Fava, 2002). Preliminary (negative) results from studies of acupuncture for bipolar depression have been presented at an international conference in 2005 but, to our knowledge, they have not yet been published. A Cochrane review (Smith and Hay, 2005) found seven reports published in English on controlled studies of the efficacy of acupuncture for major depression (Luo et al., 1985; Luo et al., 1988; Yang et al., 1994; Luo et al., 1998; Allen et al., 1998; Han et al., 2002). We identified one additional report published since the review was performed in 2004 (Quah-Smith et al., 2005). In five studies conducted in China, acupuncture or electroacupuncture was as or more efficacious than amitriptyline (150–400 mg/day) (Luo et al., 1985; Luo et al., 1988; Yang et al., 1994; Luo et al., 1998) or maprotiline (75–250 mg/day) (Han et al., 2002). In a US study, remission rates did not differ significantly after randomization to depression-specific acupuncture according to the principles of traditional Chinese, non-specific (placebo) acupuncture, or a wait-list condition (Allen et al., 1998). In a German study improvement in depression was greater with mianserin plus depression-specific or placebo-acupuncture than with mianserin alone, but there was no significant difference between depression-specific and placebo-acupuncture, suggesting that the benefits of acupuncture were due to non-specific (e.g., additional attention) effects (Roschke et al., 2000). Finally, a small Australian study found significantly

greater improvement in depressive symptoms with active laser acupuncture than with sham laser acupuncture (Quah-Smith et al., 2005). Overall, these eight trials included 547 patients but they used a variety of designs and acupuncture interventions and most of them had significant methodological flaws (Smith and Hay, 2005). Acupuncture is generally considered to be safe and well tolerated (British Medical Association Board of Science, 2000; Lytle et al., 2000; Ernst and White, 2001; White et al., 2001) and its putative complete absence of teratogenicity makes it an attractive treatment for pregnant women with depression. The risk of manic switch in depressed patients treated with acupuncture or electroacupuncture is not yet known.

Additional studies are needed before acupuncture can be recommended to patients with bipolar disorder. Given the strong non-specific effects observed with non-specific or sham (placebo) acupuncture, the control conditions used in these studies will be crucial for the meaningful interpretation of their results (Kaptchuk et al., 2006).

7. Other CAM modalities: aromatherapy massage, therapeutic massage, yoga

To our knowledge there are no data regarding the role of aromatherapy massage, therapeutic massage, yoga or aerobic exercise in the treatment of bipolar disorder. However, all of those have been reported to have beneficial effects in patients with depression; thus, we will briefly review the evidence, given the potential use of these methods during the depressive phase of bipolar illness. Aromatherapy massage has been reported to benefit patients with mild depression and anxiety in two small case series (Edge, 2003; Okamoto et al., 2005). Similarly, Chinese and Korean reports suggest that foot reflexology massage benefits depression and sleep disturbances (Song and Kim, 2006). There are also reports of beneficial use of massage therapy in depressed pregnant women (Field et al., 2004), patients with HIV infection and depression (Fulk et al., 2004), or patients with end-stage renal disease and depression (McDougall, 2005). The beneficial effects of massage therapy might be mediated through decrease of cortisol level and increase in levels of serotonin and dopamine (Field et al., 2005). Attenuation of frontal EEG asymmetry in depressed adolescents was also reported with both massage therapy and music therapy (Jones and Field, 1999).

Several studies have reported that yoga may also be of benefits in depression (Berger and Owen, 1992; Jorm et al., 2002; Woolery et al., 2004). The results of five randomized controlled trials were systematically reviewed in 2004 (Pilkington et al., 2005). All trials reported positive findings

but the variability in designs and methods (each trial utilized a different form of yoga and the severity of depression ranged from mild to severe) warrants a cautious interpretation of these results (Pilkington et al., 2005). One of these five studies compared the relative antidepressant efficacy of electroconvulsive therapy, imipramine, and yoga in patients with melancholic depression and it reported remission rates of 93%, 73%, and 67% respectively (Janakiramaiah et al., 2000).

8. Other potential uses of CAM by patients with bipolar disorder

Patients with bipolar disorder may also use CAM for specific symptoms – e.g., sleep disturbances or fatigue – or to counteract adverse effects induced by psychotropic medications – e.g., sexual dysfunction, weight gain, hair loss, memory problems, sedation, and asthenia. A discussion of the use of CAM in the treatment of these symptoms is beyond the scope of this review. However, clinicians need to be aware of the frequent use of CAM products by patients with mood disorders (Kessler et al., 2001; Roy-Byrne et al., 2005). Patients with bipolar disorder may be at particular risk for adverse effects from these products because of both the nature of their illness (Vazquez and Aguera-Ortiz, 2002) and that the multiple conventional psychotropic drugs they take that can be involved in problematic pharmacokinetic or pharmacodynamic interactions with some CAM products (Izzo, 2004). This problem is illustrated by the use of CAM products for weight loss. Several of the commercially available weight-loss supplements contain ma-huang, an herbal product derived from ephedra sinica (Pittler et al., 2005). Ma-huang may induce manic symptoms in susceptible individuals (Boerth and Caley, 2003). Other forms of herbal ephedra and ephedrine-containing food supplements can cause psychiatric, autonomic, or gastrointestinal adverse effects (Pittler et al., 2005). Ephedra has been banned by the FDA in 2004 due to its adverse cardiovascular effects (i.e., increase in blood pressure and strokes) (Food and Drug Administration, 2004). Other herbal supplements used specifically for weight loss have been associated with hepatic injury and even death (Pittler et al., 2005).

9. Conclusion

Mental health professionals need to be aware that it is likely that a fair number of their patients with bipolar disorder might use CAM interventions. Some clinicians judge these interventions to be attractive and safe alternatives or adjuncts to conventional psychotropic

medications. However, very few rigorous clinical studies have been conducted in patients with bipolar disorder. Other clinicians may consider CAM to be irrelevant but innocuous. However, this may not be the case. For example, a study of 260 Asian patent medicines found that 32% contained undeclared pharmaceuticals or heavy metal contaminants (Ko, 1998; Ernst, 2002). Still, allopathic medicine fails to provide relief in some cases that are labeled as “treatment resistant.” In these cases, it might be reasonable to include CAM therapies among treatment options, as long as their benefits outweigh their risks. In the absence of studies conducted in patients with bipolar disorder, assessment of the potential risks and benefits for these patients has to be extrapolated from the more substantial literature related to the treatment of depression. Overall, the best evidence supports the use of SJW for the treatment of mild to moderate depression. SJW may also be effective for depression. However, both of these products have the potential to induce mania and the extent of this risk still needs to be quantified. In addition, SJW can interact with a variety of medications. Evidence regarding the benefits of omega-3 fatty acids or acupuncture is inconsistent. Data regarding other CAM interventions (e.g., aromatherapy massage, massage therapy, yoga) are almost entirely lacking. Better studies are needed before CAM interventions can be recommended to patients with bipolar disorder.

Role of the funding source

Funding for this study was provided by NIMH Grant MH069430; the NIMH had no further role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute Of Mental Health or the National Institutes of Health.

Conflict of interest

Carmen Andreescu and James Emanuel have no potential conflict of interest to report. Benoit H. Mulsant has received research funds or honoraria from AstraZeneca, Bristol-Myers Squibb Company, Corcept Therapeutics, Eli Lilly and Co., Eisai, Fox Learning System, GlaxoSmithKline, Janssen-Ortho Inc., Lundbeck Inc., Janssen and Pfizer Inc.; he directly owns stock (less than \$10,000) in Akzo-Nobel N.V., Alkermes, Inc., AstraZeneca, Biogen Idec, Celsion Corp., Elan Corp., plc, Eli Lilly and Co., Forest Pharmaceuticals, The Immune Response Corporation, and Pfizer Inc.

Acknowledgements

We have no acknowledgements to report for this review article.

References

- Allen, J.J.B., Schnyer, R.N., Hitt, S.K., 1998. The efficacy of acupuncture in the treatment of major depression in women. *Psychol. Sci.* 9, 397–401.
- Alpert, J.E., Papakostas, G., Mischoulon, D., et al., 2004. *S*-adenosyl-L-methionine (SAME) as an adjunct for resistant major depressive disorder: an open trial following partial or nonresponse to selective serotonin reuptake inhibitors or venlafaxine. *J. Clin. Psychopharmacol.* 24, 661–664.
- Astin, J.A., 1998. Why patients use alternative medicine: results of a national study. *JAMA* 279, 1548–1553.
- Barnes, P.M., Powell-Griner, E., McFann, K., et al., 2004. Complementary and alternative medicine use among adults: United States, 2002. *Adv. Data* 1–19.
- Berger, B.G., Owen, D.R., 1992. Mood alteration with yoga and swimming: aerobic exercise may not be necessary. *Percept. Mot. Skills* 75, 1331–1343.
- Bilia, A.R., Gallon, S., Vincieri, F.F., 2002. Kava-kava and anxiety: growing knowledge about the efficacy and safety. *Life Sci.* 70, 2581–2597.
- Boerth, J.M., Caley, C.F., 2003. Possible case of mania associated with ma-huang. *Pharmacotherapy* 23, 380–383.
- British Medical Association Board of Science, 2000. *Acupuncture: Efficacy, Safety and Practice*. Harwood Academic, London, England.
- Calabrese, J.R., Rapport, D.J., Shelton, M.D., 1999. Fish oils and bipolar disorder: a promising but untested treatment. *Arch. Gen. Psychiatry* 56, 413–414.
- Carney, M.W., Chary, T.K., Bottiglieri, T., et al., 1989. The switch mechanism and the bipolar/unipolar dichotomy. *Br. J. Psychiatry* 154, 48–51.
- Chiu, C.C., Huang, S.Y., Chen, C.C., et al., 2005. Omega-3 fatty acids are more beneficial in the depressive phase than in the manic phase in patients with bipolar I disorder. *J. Clin. Psychiatry* 66, 1613–1614.
- Connor, K.M., Payne, V., Davidson, J.R., 2006. Kava in generalized anxiety disorder: three placebo-controlled trials. *Int. Clin. Psychopharmacol.* 21, 249–253.
- Edge, J., 2003. A pilot study addressing the effect of aromatherapy massage on mood, anxiety and relaxation in adult mental health. *Complement Ther. Nurs. Midwifery* 9, 90–97.
- Eisenberg, D.M., Davis, R.B., Ettner, S.L., et al., 1998. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* 280, 1569–1575.
- Eritsland, J., Arnesen, H., Gronseth, K., et al., 1996. Effect of dietary supplementation with *n*-3 fatty acids on coronary artery bypass graft patency. *Am. J. Cardiol.* 77, 31–36.
- Ernst, E., 2002. Toxic heavy metals and undeclared drugs in Asian herbal medicines. *Trends Pharmacol. Sci.* 23, 136–139.
- Ernst, E., 2003. Complementary medicine: where is the evidence? *J. Fam. Pract.* 52, 630–634.
- Ernst, E., Rand, J.I., Stevinson, C., 1998. Complementary therapies for depression: an overview. *Arch. Gen. Psychiatry* 55, 1026–1032.
- Ernst, E., White, A.R., 2001. Prospective studies of the safety of acupuncture: a systematic review. *Am. J. Med.* 110, 481–485.
- Escher, M., Desmeules, J., Giostra, E., et al., 2001. Hepatitis associated with Kava, a herbal remedy for anxiety. *BMJ* 322, 139.
- Fahmi, M., Huang, C., Schweitzer, I., 2002. A case of mania induced by hypericum. *World J. Biol. Psychiatry* 3, 58–59.
- Fava, M., Alpert, J., Nierenberg, A.A., et al., 2005. A double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. *J. Clin. Psychopharmacol.* 25, 441–447.
- Field, T., Diego, M.A., Hernandez-Reif, M., et al., 2004. Massage therapy effects on depressed pregnant women. *J. Psychosom. Obstet. Gynaecol.* 25, 115–122.
- Field, T., Hernandez-Reif, M., Diego, M., et al., 2005. Cortisol decreases and serotonin and dopamine increase following massage therapy. *Int. J. Neurosci.* 115, 1397–1413.
- Fleck, D.E., Keck Jr., P.E., Corey, K.B., et al., 2005. Factors associated with medication adherence in African American and white patients with bipolar disorder. *J. Clin. Psychiatry* 66, 646–652.
- Food and Drug Administration, 2004. FDA Announces Rule Prohibiting Sale of Dietary Supplements Containing Ephedrine Alkaloids Effective April 12. <http://www.fda.gov/bbs/topics/news/2004/NEW01050.html>.
- Frangou, S., Lewis, M., McCrone, P., 2006a. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. *Br. J. Psychiatry* 188, 46–50.
- Frangou, S., Lewis, M., Wollard, J., et al., 2006b. Preliminary in vivo evidence of increased *N*-acetyl-aspartate following eicosapentaenoic acid treatment in patients with bipolar disorder. *J. Psychopharmacol.*
- Freeman, M.P., 2000. Omega-3 fatty acids in psychiatry: a review. *Ann. Clin. Psychiatry* 12, 159–165.
- Fulk, L.J., Kane, B.E., Phillips, K.D., et al., 2004. Depression in HIV-infected patients: allopathic, complementary, and alternative treatments. *J. Psychosom. Res.* 57, 339–351.
- Goren, J.L., Stoll, A.L., Damico, K.E., et al., 2004. Bioavailability and lack of toxicity of *S*-adenosyl-L-methionine (SAME) in humans. *Pharmacotherapy* 24, 1501–1507.
- Gray, C.M., Tan, A.W., Pronk, N.P., et al., 2002. Complementary and alternative medicine use among health plan members. A cross-sectional survey. *Eff. Clin. Pract.* 5, 17–22.
- Grinspoon, L., Bakalar, J.B., 1998. The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *J. Psychoactive Drugs* 30, 171–177.
- Guzelcan, Y., Scholte, W.F., Assies, J., et al., 2001. [Mania during the use of a combination preparation with St. John's wort (*Hypericum perforatum*)]. *Ned. Tijdschr. Geneesk.* 145, 1943–1945.
- Hakkarainen, R., Partonen, T., Haukka, J., et al., 2004. Is low dietary intake of omega-3 fatty acids associated with depression? *Am. J. Psychiatry* 161, 567–569.
- Han, J.S., 1986. Electroacupuncture: an alternative to antidepressants for treating affective diseases? *Int. J. Neurosci.* 29, 79–92.
- Han, C., Li, X.W., Luo, H.C., 2002. Comparative study of electroacupuncture and maprotiline in treating depression. *Comb. Chin./West. J.* 22, 512–514.
- Hibbeln, J.R., 2002. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J. Affect. Disord.* 69, 15–29.
- Hirashima, F., Parow, A.M., Stoll, A.L., et al., 2004. Omega-3 fatty acid treatment and T(2) whole brain relaxation times in bipolar disorder. *Am. J. Psychiatry* 161, 1922–1924.
- Hu, J., 1996. Acupuncture treatment of manic psychosis. *J. Tradit. Chin. Med.* 16, 238–240.
- Ito, N., Nagai, T., Yabe, T., et al., 2006. Antidepressant-like activity of a Kampo (Japanese herbal) medicine, Koso-san (Xiang-Su-San), and its mode of action via the hypothalamic–pituitary–adrenal axis. *Phytomedicine*.
- Izzo, A.A., 2004. Drug interactions with St. John's wort (*Hypericum perforatum*): a review of the clinical evidence. *Int. J. Clin. Pharmacol. Ther.* 42, 139–148.
- Jacobs, B.P., Bent, S., Tice, J.A., et al., 2005. An internet-based randomized, placebo-controlled trial of kava and valerian for anxiety and insomnia. *Medicine (Baltimore)* 84, 197–207.

- Janakiramaiah, N., Gangadhar, B.N., Naga Venkatesha Murthy, P.J., et al., 2000. Antidepressant efficacy of Sudarshan Kriya Yoga (SKY) in melancholia: a randomized comparison with electroconvulsive therapy (ECT) and imipramine. *J. Affect. Disord.* 57, 255–259.
- Jones, N.A., Field, T., 1999. Massage and music therapies attenuate frontal EEG asymmetry in depressed adolescents. *Adolescence* 34, 529–534.
- Jorm, A.F., Christensen, H., Griffiths, K.M., et al., 2002. Effectiveness of complementary and self-help treatments for depression. *Med. J. Aust.* 176 (Suppl), S84–S96.
- Jussofie, A., Schmitz, A., Hiemke, C., 1994. Kavapyrone enriched extract from Piper methysticum as modulator of the GABA binding site in different regions of rat brain. *Psychopharmacology (Berl)* 116, 469–474.
- Kaneko, A., Cho, S., Hirai, K., et al., 2005. Hange-koboku-to, a Kampo medicine, modulates cerebral levels of 5-HT (5-hydroxytryptamine), NA (noradrenaline) and DA (dopamine) in mice. *Phytother. Res.* 19, 491–495.
- Kang, M., Shin, D., Oh, J.W., et al., 2005. The anti-depressant effect of Nelumbinis semen on rats under chronic mild stress induced depression-like symptoms. *Am. J. Chin Med.* 33, 205–213.
- Kaptchuk, T.J., Stason, W.B., Davis, R.B., et al., 2006. Sham device v inert pill: randomised controlled trial of two placebo treatments. *BMJ* 332, 391–397.
- Keck Jr., P.E., Mintz, J., McElroy, S.L., et al., 2006. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentaenoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol. Psychiatry* 60, 1020–1022.
- Kessler, R.C., Soukup, J., Davis, R.B., et al., 2001. The use of complementary and alternative therapies to treat anxiety and depression in the United States. *Am. J. Psychiatry* 158, 289–294.
- Ko, R.J., 1998. Adulterants in Asian patent medicines. *N. Engl. J. Med.* 339, 847.
- Kripke, D.F., 1998. Light treatment for nonseasonal depression: speed, efficacy, and combined treatment. *J. Affect. Disord.* 49, 109–117.
- Lin, P.Y., Su, K.P., 2007. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *J. Clin. Psychiatry* 68, 1056–1061.
- Linde, K., Berner, M., Egger, M., et al., 2005. St John's wort for depression: meta-analysis of randomised controlled trials. *Br. J. Psychiatry* 186, 99–107.
- Lipinski, J.F., Cohen, B.M., Frankenburg, F., et al., 1984. Open trial of S-adenosylmethionine for treatment of depression. *Am. J. Psychiatry* 141, 448–450.
- los Reyes, G.C., Koda, R.T., 2002. Determining hyperforin and hypericin content in eight brands of St. John's wort. *Am. J. Health Syst. Pharm.* 59, 545–547.
- Luo, H.C., Jia, Y.K., Li, Z., 1985. Electro-acupuncture vs. amitriptyline in the treatment of depressive states. *J. Tradit. Chin Med.* 5, 3–8.
- Luo H.C., Shen Y.C., & Jia Y.K., 1988. [Clinical study of electroacupuncture on 133 patients with depression in comparison with tricyclic amitriptyline]. *Zhong. Xi. Yi. Jie. He. Za Zhi.* 8, 77–80, 68.
- Luo, H., Meng, F., Jia, Y., et al., 1998. Clinical research on the therapeutic effect of the electroacupuncture treatment in patients with depression. *Psychiatry and Clin. Neurosci.* 52 (S), S338–S340.
- Lytte, C.D., Thomas, B.M., Gordon, E.A., et al., 2000. Electrostimulators for acupuncture: safety issues. *J. Altern. Complement Med.* 6, 37–44.
- Marangell, L.B., Martinez, J.M., Zboyan, H.A., et al., 2003. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am. J. Psychiatry* 160, 996–998.
- McDougall, G.J., 2005. Research review: the effect of acupressure with massage on fatigue and depression in patients with end-stage renal disease. *Geriatr. Nurs.* 26, 164–165.
- Melanson, S.F., Lewandrowski, E.L., Flood, J.G., et al., 2005. Measurement of organochlorines in commercial over-the-counter fish oil preparations: implications for dietary and therapeutic recommendations for omega-3 fatty acids and a review of the literature. *Arch. Pathol. Lab Med.* 129, 74–77.
- Mennini, T., Gobbi, M., 2004. The antidepressant mechanism of *Hypericum perforatum*. *Life Sci.* 75, 1021–1027.
- Mischoulon, D., Fava, M., 2002. Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence. *Am. J. Clin. Nutr.* 76, 1158S–1161S.
- Morgan, V.A., Mitchell, P.B., Jablensky, A.V., 2005. The epidemiology of bipolar disorder: sociodemographic, disability and service utilization data from the Australian National Study of Low Prevalence (Psychotic) Disorders. *Bipolar. Disord.* 7, 326–337.
- Moses, E.L., Mallinger, A.G., 2000. St. John's wort: three cases of possible mania induction. *J. Clin. Psychopharmacol.* 20, 115–117.
- Murray, C.J., Lopez, A.D., 1997. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet* 349, 1436–1442.
- National Center for Complementary and Alternative Medicine – National Institutes of Health, 2002. What is Complementary and Alternative Medicine. <http://nccam.nih.gov/health/whatiscam/#sup1>.
- Nemets, B., Stahl, Z., Belmaker, R.H., 2002. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am. J. Psychiatry* 159, 477–479.
- Nierenberg, A.A., Burt, T., Matthews, J., et al., 1999. Mania associated with St. John's wort. *Biol. Psychiatry* 46, 1707–1708.
- Okamoto, A., Kuriyama, H., Watanabe, S., et al., 2005. The effect of aromatherapy massage on mild depression: a pilot study. *Psychiatry Clin. Neurosci.* 59, 363.
- Osher, Y., Bersudsky, Y., Belmaker, R.H., 2005. Omega-3 eicosapentaenoic acid in bipolar depression: report of a small open-label study. *J. Clin. Psychiatry* 66, 726–729.
- Peet, M., Horrobin, D.F., 2002a. A dose-ranging exploratory study of the effects of ethyl-eicosapentaenoate in patients with persistent schizophrenic symptoms. *J. Psychiatr. Res.* 36, 7–18.
- Peet, M., Horrobin, D.F., 2002b. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch. Gen. Psychiatry* 59, 913–919.
- Pilkington, K., Kirkwood, G., Rampes, H., et al., 2005. Yoga for depression: the research evidence. *Journal of Affective Disorders* 89, 13–24.
- Pittler, M.H., Ernst, E., 2003. Kava extract for treating anxiety. *Cochrane. Database. Syst. Rev.* CD003383.
- Pittler, M.H., Schmidt, K., Ernst, E., 2005. Adverse events of herbal food supplements for body weight reduction: systematic review. *Obes. Rev.* 6, 93–111.
- Polyakov, S.E., 1988. Acupuncture in the treatment of endogenous depressions. *Zh Neuropat Psikhiatr Korsakova* 21, 36–44.
- Post, R.M., Leverich, G.S., Altshuler, L.L., et al., 2003. An overview of recent findings of the Stanley Foundation Bipolar Network (Part I). *Bipolar. Disord.* 5, 310–319.
- Quah-Smith, J.I., Tang, W.M., Russell, J., 2005. Laser acupuncture for mild to moderate depression in a primary care setting—a randomised controlled trial. *Acupunct. Med.* 23, 103–111.

- Roschke, J., Wolf, C., Muller, M.J., et al., 2000. The benefit from whole body acupuncture in major depression. *J. Affect. Disord.* 57, 73–81.
- Roy-Byrne, P.P., Bystritsky, A., Russo, J., et al., 2005. Use of herbal medicine in primary care patients with mood and anxiety disorders. *Psychosomatics* 46, 117–122.
- Shibayama, Y., Ikeda, R., Motoya, T., et al., 2004. St. John's wort (*Hypericum perforatum*) induces overexpression of multidrug resistance protein 2 (MRP2) in rats: a 30-day ingestion study. *Food Chem. Toxicol.* 42, 995–1002.
- Simopoulos, A.P., 2003. Importance of the ratio of omega-6/omega-3 essential fatty acids: evolutionary aspects. *World Rev. Nutr. Diet.* 92, 1–22.
- Smith, C.A., Hay, P.P., 2005. Acupuncture for depression. *Cochrane Database. Syst. Rev.* CD004046.
- Song, R.H., Kim, D.H., 2006. The effects of foot reflexion massage on sleep disturbance, depression disorder, and the physiological index of the elderly. *Taehan Kanho. Hakhoe. Chi* 36, 15–24.
- Stoll, A.L., Severus, W.E., Freeman, M.P., et al., 1999. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen. Psychiatry* 56, 407–412.
- Su, K.P., Huang, S.Y., Chiu, C.C., et al., 2003. Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. *Eur. Neuropsychopharmacol.* 13, 267–271.
- Tanskanen, A., Hibbeln, J.R., Hintikka, J., et al., 2001. Fish consumption, depression, and suicidality in a general population. *Arch. Gen. Psychiatry* 58, 512–513.
- Vazquez, I., Aguera-Ortiz, L.F., 2002. Herbal products and serious side effects: a case of ginseng-induced manic episode. *Acta Psychiatr. Scand.* 105, 76–77.
- Wheatley, D., 2005. Medicinal plants for insomnia: a review of their pharmacology, efficacy and tolerability. *J. Psychopharmacol.* 19, 414–421.
- White, A., Hayhoe, S., Hart, A., et al., 2001. Adverse events following acupuncture: prospective survey of 32 000 consultations with doctors and physiotherapists. *BMJ* 323, 485–486.
- Woolery, A., Myers, H., Sternlieb, B., et al., 2004. A yoga intervention for young adults with elevated symptoms of depression. *Altern. Ther. Health Med.* 10, 60–63.
- Yang, X., Liu, X., Luo, H., et al., 1994. Clinical observation on needling extrachannel points in treating mental depression. *J. Tradit. Chin Med.* 14, 14–18.
- Zanarini, M.C., Frankenburg, F.R., 2003. Omega-3 fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *Fam. J. Psychiatry* 160, 167–169.
- Zhang, Z.J., Kang, W.H., Tan, Q.R., et al., 2005. Adjunctive herbal medicine with carbamazepine for bipolar disorders: a double-blind, randomized, placebo-controlled study. *J. Psychiatr. Res.*
- Zhang, Z.J., Kang, W.H., Li, Q., et al., 2007. The beneficial effects of the herbal medicine Free and Easy Wanderer Plus (FEWP) for mood disorders: double-blind, placebo-controlled studies. *J. Psychiatr. Res.* 41, 828–836.