40
Complementary and Alternative Medical Treatment for Depression

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Abstract

As the mainstream medical world is confronted with the dramatic increases in the utilization of complementary and alternative medicine (CAM) therapies, much is unknown regarding how to adequately consider these alternative treatments. There is little scientific justification to support the use of the vast array of alternative options, but these treatments are readily available to the public and CAM professionals. The public has been choosing to use dietary supplements, which has driven the increased utilization of CAM treatments in the past decade. This chapter discusses CAM treatments for major depression, but the primary focus is on dietary supplements. It is important to discuss how CAM clinicians ascertain that alternative treatment modalities are appropriate and then ascertain factors/symptoms in depressive illness that are most relevant when choosing from a myriad of treatment options available. It is important to mention that a substantial portion of the public has been utilizing dietary supplements without consulting CAM or non-CAM clinicians.

40.1
Introduction

40.1.1
Definitions

Familiarity with the following frequently used terms is helpful to understanding this chapter.

Complementary and alternative medicine: The National Center for Alternative and Complementary Medicine (NCCAM) refers to complementary and alternative medicine (CAM) as a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine

Biology of Depression. Edited by Julio Licinio

ISBN: 3-527-30785-0

[1]. 'Complementary' describes a therapy that is used 'in addition to', and 'alternative' therapy is one that is used 'instead of' conventional therapy. CAM practitioners may be doctors of conventional medicine (see below) or may be doctors of naturopathic medicine (ND), nutritionists, herbalists, Chinese medicine practitioners, chiropractors, energetic healers, and so forth. The NCCAM classifies CAM treatments into seven categories: (1) alternative systems of medical care; (2) bioelectromagnetic therapies; (3) diet, nutrition and lifestyle changes; (4) herbal medicine; (5) manual healing methods; (6) mind–body medicine; and (7) pharmacological and biological therapies. Therefore, CAM therapies may incorporate nutrient therapies, botanical medicines, dietary changes, Ayurvedic medicine, energy healing, hypnosis, acupuncture, spinal manipulation, animal-assisted therapy, physical medicines, and so forth.

Ayurveda: An ancient comprehensive system of medicine that was developed in India over 5000 years ago. It places emphasis on body, mind, and spirit with the goal of restoring the natural harmony of the individual. A patient's 'constitution' can be classified into one of three types (Vata, Pitta, or Kapha); these metabolic body types become the foundation for a specific treatment plan designed to guide the individual back to a state of harmony with his/her environment.

Conventional medicine: Medicine as practiced by holders of medical doctor (MD) or doctor of osteopathy (DO) degrees and by their allied health professionals, such as physical therapists, psychologists, and registered nurses. Other terms for conventional medicine include allopathic, Western, mainstream, orthodox, and regular medicine and biomedicine. Some conventional medical practitioners are also practitioners of CAM [1].

Dietary supplement: A product that is ingested and intended to supplement the diet and, among other requirements, it contains a 'dietary ingredient' that was defined by Congress in the Dietary Supplement Health and Education Act (DSHEA) of 1994. The dietary ingredient may include several products, such as vitamins, minerals, herbs or other botanicals, amino acids, and enzymes. Dietary supplements (DS), which can be found in many forms, including tablets, capsules, liquids, and bars, are classified under a special category of 'foods'; the DSHEA requires that every supplement be labeled as a DS, but these products are not subject to the stringent U.S. Food and Drug Administration (FDA) safety and efficacy testing requirements that are required for drugs. DS are by nature heterogeneous products; therefore, within a particular DS product type, there are many different types of products and many different forms in which the products are made available.

Integrative Medicine: Combination of mainstream medical therapies and CAM therapies [1].

Naturopathic Medicine: Founded upon a holistic philosophy, naturopathic medicine combines safe and effective traditional therapies with the most-current advances

in modern medicine. Naturopathic medicine is appropriate for the management of a broad range of health conditions affecting all people of all ages. Naturopathic physicians (ND) are the highest-trained practitioners in the broadest scope of naturopathic medical modalities. In addition to the basic medical sciences and conventional diagnostics, naturopathic education includes therapeutic nutrition, botanical medicine, homeopathy, natural childbirth, classical Chinese medicine, hydrotherapy, naturopathic manipulative therapy, pharmacology, and minor surgery [2].

40.1.2 Complementary and Alternative Medicine Use today

Despite a long history of folk and anecdotal use, CAM modalities have received relatively little attention in the conventional medical world until recently. Modalities such as botanical medicines, lifestyle, nutrition, and acupuncture have silently played a role in the treatment of depressive illness, as they are clearly sought by the public, and the perception has been that their utilization has increased [3, 4].

However, only lately has the medical literature begun to be confronted with the ubiquity with which CAM modalities have been utilized and their possible impact on conventional medical treatments. The Centers for Disease Control (CDC) and Prevention's National Center for Health Statistics recently reported that 62% of adults employed some form of CAM therapy during the past 12 months. Modalities that were most relied on, in order of popularity, included prayer, natural products (nutrient therapies, botanicals), deep breathing, meditation, chiropractic care, yoga, massage, and dietary changes [6]. This corroborates recent data, which finds prayer to be the most popular alternative therapy, as 35% of the population makes use of prayer for their health concerns [5]. CAM was most often used to treat anxiety or depression, back pain or back problems, head or chest colds, neck pain or neck problems, and joint pain or stiffness [6].

Eisenberg's national survey documented that Americans spent $629 million on CAM treatments in 1997. Out of those surveyed, 42.1% had used some type of alternative treatment. Botanical medicines, massage, vitamins, support and self-help groups, folk remedies, energy healing, and homeopathy were the primary therapies reported with the greatest frequency. Again, depression and anxiety were noted as a primary condition for which those surveyed used CAM applications. Other conditions included back problems, headaches, and chronic medical illness [7]. Thirty-two percent of the men and women surveyed used an alternative therapy to treat a condition for which they were concurrently seeing a physician. Interestingly and importantly, fewer than 40% of these people disclosed to their physician that they were using another type of therapy. This is vital to keep in mind, for in these patients preventable untoward interactions between complementary and conventional therapies may be more likely to occur and progress be unrecognized.

The choice of CAM treatment modality seem to be population-dependent, as age group, specific medical condition, and geographic location may predispose a particular set of population or CAM practitioners to gravitate toward preferentially

employing a particular form of therapy or not to use any at all. Conversely to Eisenberg's work, one study of an elderly population found a decreased incidence of alternative medicine use. Out of 655 elderly living in an urban center, the overall use of at least one alternative medicine was 29.5%; among these, botanical (47%) and acupuncture (34%) were the most frequently cited therapies; 3.7% of the sample used exclusively alternative medicines [8]. The reasons for decreased CAM use in the elderly may include decreased education about these therapies, decreased access, or unwillingness to try unconventional modes of treatment. One study suggests that the use of CAM may be a indicator of the presence of more severe psychological stress among patients [9]; that study revealed that 32% of breast cancer patients used CAM therapy and that a large majority of patients who used spiritual healing had depressive symptoms.

Although there may not be enough information to develop a complete world map of CAM usage at this time, it is clear that the utilization of these therapies varies greatly. For example, a survey of 7485 people in Canberra, Australia, showed that just 2.28% used sole CAM therapies to treat their depression or anxiety, while merely 0.59% used integrated conventional medications with CAM therapies [10].

Literature supporting the use of alternative therapies for mild-to-moderate depression has been coalescing [11]. Favorable reviews regarding the use of CAM is becoming more common as published research finds "the potential for doing good is greater than the potential for doing harm" [12]. Although many of the therapies that are said to benefit depression appear to be safe, it is important to note that serious neuropsychiatric side effects and interactions have been reported [13]. Although many CAM therapies for depression are probably safe and effective for yet-to-be-identified subgroup(s) of depressed individuals, more research is required to understand their mechanisms of actions and to understand whether the placebo effect plays a role in these treatments.

40.1.3 Public Health Impact

Herbal or botanical supplements are taken daily by millions of people, in spite of a paucity of data on their potential mechanisms of action. The DS industry is a multibillion dollar industry that has recently been growing exponentially. The full range of DS products sales has been reported to have reached $17.1 billion in 2000 [1]. The U.S. FDA published an economic characterization of the DS industry in 1999 [14], and most sources agree that this industry has grown rapidly and will continue to do so in the near future. The estimated retail sales of DS products vary widely, but consumer spending has been reported to have doubled between 1994 and 2000 and continues to grow at more than 10% per year [15]. In addition, the distribution channels have diversified rapidly, as grocery stores, drugstores, and direct selling, mail-order, and online marketers are increasing the range of DS products they carry. Consumer demands have driven larger pharmaceutical companies to enter the market by buying DS firms.

Herbal and botanical supplement sales totaled $3 billion, for a 28% share of the DS market; their growth rate of 20% from 1995 to 1996 was the highest of all DS products. Since the DSHEA has classified DS as a new category of food, DS have remained largely unregulated, and consequently consumers have been poorly informed about safety and efficacy of alternative treatments. The World Health Organization (WHO) has recognized this problem and has sounded the alarm: in June 23, 2004 it announced new guidelines to promote proper use of alternative medicines (http://www.who.int/mediacentre/releases/2004/pr44/en/index1.html) [16]. That WHO Report warned that growing use of alternative medicine poses global health risks and urged governments around the world to intensify oversight of this industry. The NCCAM published a nationwide survey in May 27, 2004, [17] which found that 36% of American adults use some form of alternative medicine or treatment; the number is even higher for other high-income developed countries. In developing nations, up to 80% of the population may rely on traditional or alternative medicine for their primary medical care (WHO).

40.1.4 CAM Research and Practice

In the interest of safety and time efficacy of CAM therapies, emphasis has been placed on the need to hold CAM therapies to the same scientific standards as conventional medicine [18]. It is very important to characterize the possible toxicity of alternative therapies and to evaluate CAM compounds for clinical efficacy; but, as DS are a category of 'food', their clinical efficacy does not need to be proven. The CAM community has been concerned about not loosing sight of its own mission, while applying allopathic conventional standards to nonconventional therapeutics, as detailed in the statement below made by Joseph E. Pizzorno, ND, former appointee to the White House Commission on Complementary and Alternative Medicine Policy [19]:

> "CAM is about a fundamentally different approach to health and healing that comprehensively addresses promotion of the health of the patient, not simply the temporary relief of the symptoms of disease that characterizes the health-care system today. [We need] to research systems of healing, rather than simply 'green' drugs (for example, substituting a 'natural drug' for a synthetic drug). Comparing the efficacy of St. John's wort to conventional antidepressant medication is of limited value. This is not how CAM is practiced! Worse, it continues the failing medical philosophy of treating the symptom rather than the person, and not addressing the cause(s) of his disease. When I see a patient with depression, I treat that person comprehensively, searching deeply for the fundamental cause of his or her disease. Is there a nutritional deficiency? Has he been exposed to a neurotoxic chemical? Has she disrupted her neurochemical balance by excess sugar consumption? Has he developed inappropriate learned behavior? Correcting these kinds of causes is curative. St. John's wort is not a curative treatment, but rather a symptomatic one –

> my last choice, not my first! This is not to dismiss the fact that St. John's wort is a very useful natural therapy in the care of the depressed patient. But this herb by itself does not fully utilize the power of integrative medicine."

The majority of scientific information available to this field has emerged from conventional medical research that has not utilized a systems-integrated approach toward healing. It is relevant to point out that CAM professionals working with depressed patients try to adopt a multidimensional approach aimed at the perceived main 'causative' factors of this condition and not just at symptom relief; thus, they try to deliver what they believe to be the most complete therapy that will have lasting clinical results. This chapter discusses CAM treatment approaches and focuses on DS treatments.

40.2 Treatment Approach

It is paramount to keep in mind the point of view of an integrative health practitioner, who seeks possible 'causative' factors of depression for each individual, which are thought to be unique and multifactorial. This integrative thinking recognizes that the alleged 'causes' of depression for one individual may be different than those for another patient. The CAM practitioner takes a careful history of the condition in a process that is parallel to the approach taken in conventional medicine. Several medical conditions may be associated with the presentation of major depressive symptoms, which they have been addressed in Chapter ■■. The CAM practitioner also recognizes that stabilization of chronic or acute conditions is also helpful to the improvement of depressive symptoms. It is important to note that CAM practitioners will treat only mild-to-moderate cases of depression and refer severe cases and cases with a perceived organic cause to conventional medicine clinicians. CAM professionals pay special attention to lifestyle factors (see below, Section ■■), largely based on common sense; some of these factors have not been fully scrutinized in the medical literature.

40.2.1 When CAM Therapies Are Not Appropriate as a First Line of Treatment

In the interests of safety and practicality, pharmaceutical medications should be considered as the first line therapy in any instance in which:

- There is immediate concern of harm to self or harm to others (suicidal ideation, planning, history of harming self and others, threats to do so, and so forth).
- The patient is not able to function in a capacity necessary to perform basic functions such as work to feed or house self or family and/or to take care of another person who relies on the patient for survival in a situation in which no other option exists.

Once the patient has been stabilized with respect to the above conditions, CAM therapies that address lifestyle, psychological/spiritual, as well as nutrient and supplemental therapies may be considered for a longer-term treatment. Preferably, team management by the patient's pharmaceutical prescribing doctor, psychologist, and CAM practitioner(s) will afford the best overall care and enable the comanagement needed to consider discontinuation of medications. This possibility will be more appropriately realized once other lifestyle, psychological, physiological, and nutritional factors are successfully addressed.

Two possible exceptions to the above conditions would be pregnant and breastfeeding women. Incidences of withdrawal effects in newborns have recently prompted the Food and Drug Administration to caution women about the use of antidepressants during the third trimester of pregnancy. Nortriptyline, paroxetine, and sertraline may be preferred choices in breastfeeding women [20]. But overall, since there is a striking lack of clinical evidence about the safety of psychotropic medications during breastfeeding [21], it is advisable to carefully consider the pros and cons of using antidepressants for the duration of breastfeeding. Of course, untreated depression in pregnant and breastfeeding patients can also pose great risk for both the mother and child; therefore, a careful case-by-case evaluation of the pharmaceuticals chosen as well as the specific circumstances of depression is required.

40.2.2 When CAM Therapies Can Be Considered as a First Line of Treatment

A team approach involving a doctor experienced and licensed to prescribe pharmaceutical interventions, a psychologist/therapist, and a CAM practitioner well versed in the use of natural and alternative modalities all working together would combine the best of all worlds regarding optimal patient care. Once a decision is made that the patient does not meet the criteria outlined above that necessitate first-line pharmaceutical intervention, the CAM practitioner should feel comfortable trying alternative and holistically minded modalities, while remaining vigilant to changes in the patient's condition that could lead to him or her meeting the above criteria at a later time.

It is clear that clinical studies conducted primarily in hospital settings have demonstrated efficacy for patients with moderate-to-severe major depression. However, the vast majority of patients treated for depression occur in general-practice settings, where most of these patients do not meet the diagnostic criteria for major depression [22]. From a naturopathic perspective, this is the situation in which CAM practitioners could probably do the most good by intervening with more holistic options, while keeping in mind that antidepressants may be implemented as a final resort if needed.

40.3 CAM Therapies

The list of all available CAM therapy is long and beyond the scope of this chapter. While focusing on treatment alternatives with DS, I try to provide an objective summary of the research available regarding various alternative therapies and attempt to compare them with conventional therapies.

40.3.1 Botanical Medicines

Known as herbs in the mainstream community, the recognition of botanical medicines has grown considerably in the last decade. Eisenberg found that use of herbal medicine rose from 3% to 12% from 1990 to 1997 [7]. Although there are a plethora of botanicals that are used to modify central nervous system function, those listed below represent the ones most studied in the medical literature.

40.3.1.1 Hypericum perforatum (St. John's Wort)

As one of the best-studied botanicals of all time, St. John's wort (SJW) is notable for its ability to treat mild-to-moderate depression [23, 24] and is also known to be safe and effective for children [25]. As a result, SJW has become very popular in the U.S., where it is available over the counter. In Germany, physicians prescribe SJW to patients with mild-to-moderate depression [26].

The possible action of SJW stems in part from its hypericin and hypericin-like constituents, which may act on acetylcholinesterase by decreasing the degradation rate of acetylcholine [27]. Sedative actions come from the hypericins, biflavones, and hyperforin. Other reports demonstrate a serotonergic activity [28], by which it can act as a weak serotonin-reuptake inhibitor (SSRI) that leads to fewer side effects [29]. In addition, sigma 1 receptors, which are affected by antidepressant medications in animal studies, may also be affected by SJW [30]. Most likely, the demonstrated efficacy of this botanical in treating depression is through its synergistic effects, orchestrated by the multitude of components in the whole herb working both within and peripheral to the central nervous system.

A meta-analysis of 23 randomized trials which included 1757 outpatients with mainly mild or moderately severe depressive symptoms found that *Hypericum* extracts were significantly superior to placebo and similarly effective as standard antidepressants. Side effects occurred in 19.8% patients on *Hypericum* and 52.8% patients on standard antidepressants [23], and data analysis revealed a dropout rate of 0.8% for SJW and 3.0% for standard antidepressant drugs due to side effects.

Two well publicized clinical studies have suggested that SJW is ineffective in treating depression [31]. One 8-week trial employed suboptimal doses of SJW, using 900 mg d^{-1} for patients with severe depression. If there was no response, doses were increased to 1200 mg d^{-1}. (In a previous study of severe depression, patients improved significantly on SJW, compared to placebo and the antidepressant drug imipramine, on a dose of 1800 mg d^{-1} [32, 33].) It is worth mentioning the role of

a possible conflict of interest in that study, given that that trial was funded by a drug company that manufactures antidepressant medications. In light of a previous history of effective SJW trials, it is dubious whether those results accurately reflect the clinical ability of this botanical.

A second 8-week study made a similar suboptimal dosing error and consequently deemed St. John's wort to be ineffective. A valuable note in this study is that the comparison drug sertraline, a drug with a much stronger side-effect profile than *Hypericum*, was not any more effective than SJW or the placebo, which leads to concerns about the overall design of the study [34].

The action of SJW has been well characterized in direct comparisons with leading antidepressant medications [35–37]. In a randomized controlled double-blind trial, 70 patients suffering from mild-to-moderate depression received one tablet of either SJW extract or fluoxetine twice a day for 6 weeks. Patients were rated by the 17-item Hamilton Rating Scale for Depression (HAMD) and the von Zerssen depression scale (ZDS). HAMD scores significant decreased ($p < 0.001$) in the SJW group (50%) and in the fluoxetine group (58%), and ZDS also decreased in both treatments (42% and 52%, respectively). Assessments by physicians and patients indicated considerable improvement with no between-treatment differences [35]. The conclusion of that study is that SJW was therapeutically equivalent to fluoxetine and is therefore a reasonable alternative to synthetic antidepressants. *Hypericum* extract has similarly been tested and showed an efficacy similar to that of sertraline in the treatment of mild-to-moderate depression in a small group of outpatients [36]. Efficacy and tolerability of SJW was also compared with imipramine and was equivalent to that of the drug in treating mild-to-moderate depression. In addition, patients tolerated SJW better than imipramine [37].

In a review of over 3000 depressed patients spanning 34 double-blind trials, the effective dosage level of SJW for mild-to-moderate depression was between 500 and 1000 mg of standardized alcohol extract per day [38]. For patients with preexisting conductive heart dysfunction or elderly patients, high-dose *Hypericum* extract has found to be safer with respect to cardiac function than tricyclic antidepressants [39].

The side-effect profile of SJW extract is minor, especially when compared to the well known side effects of antidepressant medications [40]. Due to its lack of monoamine oxidase (MAO) inhibition, SJW is not considered to interact negatively with MAO-inhibiting drugs or tyramine-containing foods. However, it has been shown important SJW–drug interactions may occur. SJW can reduce the circulating levels of certain drugs [41–44] (Table 40.1). Synergistic therapeutic effects may also lead to complications and unfavorable treatment outcome. SJW is a potent inducer of cytochrome p450 (CYP) enzymes, particularly CYP 3A4 and/or P-glycoprotein, and it may also inhibit or induce other CYPs [45].

Although SJW induces photosensitivity in some patients, this not likely to happen with standard dosages; it has occurred mainly in HIV patients using larger than normal quantities for an antiviral effect [46]. SJW is not recommended for use during pregnancy, because its safety in pregnancy has not been studied. A study of 33 mothers who used SJW while nursing found no significant difference in the

Table 40.1 Saint John's wort (SJW)–drug interactions

1. SJW decreases the blood concentrations of the following agents:	
Anticancer drugs:	irinotecan and its active metabolite SN-38
Anticoagulants:	phenprocoumon and warfarin
Antidepressants:	amitriptyline
Anti-HIV agents:	protease inhibitor indinavir
	reverse transcriptase inhibitor nevirapine
Antihistamines:	fexofenadine
Bronchodilators:	theophylline
Cardiovascular drugs:	digoxin and simvastatin
Immune suppressants:	cyclosporine and tacrolimus
Opiates:	methadone
Sedatives:	midazolam
2. SJW may cause:	
Serotonin syndrome when coadministered with selective serotonin-reuptake inhibitors (e.g., sertraline, paroxetine)	
Breathrough bleeding and unplanned pregnancies when used concomitantly with oral contraceptives	
Hypoglycemia when used concomitantly with tolbutamide	
3. SJW does not alter the pharmacokinetics of:	
Anticonvulsants:	carbamazepine
Cardiovascular drugs:	pravastatin
Cough medication:	dextromethorphan
Immunosuppressants:	mycophenolic acid

frequency of maternal report of decreased milk production among the groups, nor was a difference found in infant weight over the first year of life [47].

The most commonly recommended dose of SJW is 300 mg of standardized extract, three times daily, for mild-to-moderate depression [38]. A number of CAM practitioners use the upper therapeutic range, which approaches 1800 mg d^{-1}, for moderate-to-severe illness. Of course, when the CAM practitioner is considering *Hypericum* therapy, he or she should always consider lifestyle, nutrient, and other factors described later in this chapter to work on simultaneously so as to achieve the best results. Symptoms indicating excessive levels of serotonin should also be considered and monitored when using SJW with SSRIs, tryptophan, or 5-HTP.

40.3.1.2 **Gingko biloba (Gingko)**

Although SJW is a clear favorite botanical treatment option for depression, ginkgo is known for its antioxidants/free radical scavenging effects, neuroprotective/antiplatelet aggregating actions, beneficial effects against ischemia/reperfusion injury, hypoxia, cerebrovascular and cardiovascular diseases, cognitive deficit and dementia and has been found to normalize stress-elevated alterations in levels of brain catecholamines, serotonin, and plasma corticosterone [48].

Given its reputation for neuroprotective and cerebrovascular effects, ginkgo may be most useful for depressive symptoms associated with and/or resulting from vascular events. This type of mood disorder, due to a general medical condition,

occurs principally the elderly and is caused by acute or chronic damage to the cerebral vascular system.

Although SJW may be best for those under 50 years of age, CAM practitioners may want to work with ginkgo first as a means to treat older patients with a clinical presentation suggestive of major depressive-like episode secondary to cerebrovascular disease. *Gingko biloba* extract may be used at a dosage of 80 mg three times a day (24% gingko flavonglycosides) [102].

Gingko biloba leaf extract is quite low in toxicity – a review of 44 double-blind trials having nearly 10 000 participants showed only mild discomfort of the gastrointestinal tract, headache, or dizziness in a total of 34 cases. In contrast, gingko fruit pulp exposure should be avoided, because it can cause severe allergic reaction and gastrointestinal irritation [102].

40.3.1.3 **Lavendula angustifolium (lavender)**

Lavender is used principally as an aromatic essential oil for relaxation. In a single-blind randomized control trial, 80 women who took daily baths with lavender oil experienced improved mood, reduced aggression, and a more positive outlook [49]. Furthermore, the combination of lavender (60 drops d^{-1} of a lavandula tincture) and imipramine (100 mg d^{-1}) was found to be more effective in the treatment of depression than either treatment alone, according to a double-blind randomized control trial. The findings of this study suggested that taking a moderate amount of lavender may help reduce the amount of tricyclic antidepressants needed to treat depression, leading to fewer side effects [50].

40.3.2 **Supplemental Therapies**

Both botanical and other alternative therapies are listed in Table 40.2.

40.3.2.1 **Chromium**

It has been observed that poor glycemic control is correlated with moderate-to-severe depression [51]. Chromium is an essential trace element that is known as a component of the body's glucose tolerance factor and may be a useful means to balance insulin levels. Chromium's mode of operation may also be by alteration of brain serotonin levels [52], as well by increasing insulin sensitivity [53].

A placebo-controlled double-blind pilot study of chromium piccolinate was conducted in 15 patients with atypical types of major depressive disorder, a type of depression that constitutes more than one-fifth of all cases of depression. Ten patients started with a dose of 400 μg, which was increased to 600 μg. The other five patients took a placebo. Seventy percent of the patients on chromium responded positively to the treatment. This study had some unusual results, as none of the placebo patients showed improvement. Other outcomes were consistent with greater effect of chromium. Three patients on chromium failed to show any improvement. Chromium piccolinate was well tolerated, with no attrition due to side effects [54]. With no known side effects at the standard dosage of 200 μg d^{-1}, chromium could

Table 40.2 Brief review of natural supplements for depression

Botanical	***Dosage***	***Possible Mechanism***	***Side Effects and Contraindications***
Hypericum perforatum (St. John's wort)	300–600 mg of the extract TID	Reduces the degradation rate of acetylcholine, sedative actions, weak serotonergic activity, sigma 1 receptor blockade	Minor side effect profile, but interactions can change the bioavailability of many drugs (Table 40.1); photosensitivity at very high doses
Gingko biloba	80 mg TID	Antioxidant, cerebrovascular protection, etc.	Rare mild gastrointestinal complaints from the extract; fruit is toxic
Supplement	Dosage	Possible Mechanism	Side Effects and Contraindications
Chromium	200 μg qd	Glucose balance, serotonin modulation	None known at therapeutic dosages
Fish oil (omega-3 fatty acids)	1 tablespoon of fish oil qd, or 2 g DHA qd	Platelet clotting ability, inhibits sympathoadrenal activation and normalizes membranes	Side effects of mild reflux and gastrointestinal disturbances; consider TT, PTT, and INR monitoring for patients on anticlotting medications.
Folic Acid	0.5–1.0 mg qd	Lowers homocysteine	Contraindicated with methotrexate for cancer treatment or antiseizure medications
Inositol	4–12 g qd	Serotonin and acetylcholinergic modulation	None known at therapeutic dosages
Melatonin	0.5–5 mg hs	Circadian rhythm restoration and antioxidant	Side effects of some waking drowsiness; contraindicated in nocturnal asthmatics
SAMe	See dosing schedule in Section 5.3.7	Methylation; may help lower homocysteine levels	Nausea, mild gastrointestinal disturbances, agitation
Selenium	200 μg qd	Antioxidant, helps convert T4 to T3, enhances immunity	Can cause brittle nails in high doses

Table 40.2 (continued)

Botanical	*Dosage*	*Possible Mechanism*	*Side Effects and Contraindications*
L-tryptophan	0.5–1.0 g qd	Serotonin precursor	Side effect of possible serotonin syndrome when used with other SSRIs or St. John's Wort
5-HTP	100–200 mg TID	Serotonin precursor	Possible serotonin syndrome when used with other SSRIs or St. John's wort
Vitamin E	400 IU qd	Antioxidant	None known at therapeutic dose
Zinc	25 mg qd	Neurologic and immune modulator	Long-term supplementation may deplete copper

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be used as a reasonable treatment choice for depressed patients, especially for those exhibiting blood sugar dysregulation.

40.3.2.2 Fish Oils and Fatty Acids

Two types of omega-3 fatty acids are eicosapentanoic acid (EPA) and docosahexanoic acid (DHA). These are found in seafood, especially in wild salmon, striped bass, mackerel, rainbow trout, halibut, and sardines. There is ample evidence that shows correlations between low seafood consumption and higher rates of depressive illness. For instance, lower DHA content in mother's milk and lower seafood consumption were associated with higher rates of postpartum depression [55]. Conversely, geographic areas where consumption of DHA is high are associated with decreased rates of depression. Individuals with major depression have marked depletions in omega-3 fatty acids (especially DHA) in erythrocyte phospholipids compared with controls. These data suggest that DHA may be associated with depression, and the limited data available on supplementation with DHA or other omega-3 fatty acids seem to support the hypothesis that DHA may have psychotropic effects [56].

Possible mechanisms of action include the ability of omega-3 fatty acids to positively affect the cardiovascular system and adrenal function and to normalize membranes of brain tissues. Omega-3 fats reduce the clotting ability of platelets and so can potentially decrease the incidence of heart attacks and strokes. It thus seems reasonable that the relationship between depressive disorders and cardiovascular disease could be intertwined with omega-3 fatty acid deficiency and elevated homocysteine levels [57]. Omega-3 fatty acids acts mechanistically on the central nervous system by inhibiting sympathoadrenal activation elicited by mental stress [58]. Finally, one hypothesis is that omega-3 fatty acids can normalize the altered membrane microstructure and neurotransmission in patients with depression [59]. These altered structures are thought to be a contributing factor in depressive pathogeneses.

A number of studies support the use of fish oil for depression as well as for bipolar disorder [60]. Furthermore, there is evidence that fish oil may benefit people who fail to respond to standard medications. A study of 70 patients with persistent depression despite ongoing treatment with an adequate dose of a standard antidepressant were found to benefit from 1 g d^{-1} of ethyl-eicosapentaenoate. Strong beneficial effects were indicated by using the HAMD, Montgomery–Asberg Depression Rating Scale, and Beck Depression Inventory to monitor depression, anxiety, sleep, lassitude, libido, and suicidality [61].

In other studies, the benefit was not as clear. In one study, employing DHA for postpartum depression, supplementation of approximately 200 mg d^{-1} for 4 months after delivery prevented the usual decline in plasma phospholipid docosahexaenoic acid content in women who breastfeed. However promising this may be, this supplementation did not influence self ratings of depression or diagnostic measures of depression or information processing [62]. A second randomized control trial involved 36 depressed patients who were randomly assigned to receive 2 g d^{-1} DHA or placebo for 6 weeks. In this work, response rates were 27.8% in the DHA group and 23.5% in the placebo group, numbers that did not achieve statistical significance [63].

Some studies have also evaluated the use of a fatty acid supplement in addition to a conventional antidepressant regimen. One randomized controlled double-blind trial of 22 patients with major depressive disorder found significant benefits from the addition of omega-3 fatty acid compared with placebo. These benefits were apparent by the third week of treatment [64].

Although fish oil is quite safe [65], some people taking fish oil dietary supplements may experience nausea, loose stools, and 'fishy' breath from high doses. Because of a possible concern of excess antiplatelet activity when used in combination with anticlotting drugs, it seems to be best to monitor thrombin time, prothrombin time, and INR closely if the patient is on an anticlotting medication. Also of note, CAM practitioners should prescribe only high-quality pharmaceutical-grade fish oils, because the lower-quality versions may have an increased liability to rancidity and may contain higher amounts of toxins and impurities.

40.3.2.3 **Folate**

Although its effects in depression are not fully elucidated, folate may modulate serotonergic or catecholaminergic functions [67] and may decrease plasma homocysteine levels [66]. Observed deficiencies in these have been correlated with depressive symptoms in bulimia nervosa [67]. The relationships among levels of folate, vitamin B12, and homocysteine and response to fluoxetine (20 mg d^{-1} for 8 weeks) treatment have been examined in 213 outpatients with major depressive disorder [68]. Subjects with low folate levels were more likely to have melancholic depression and were significantly less likely to respond to fluoxetine. There might be a correlation between low folate levels and poorer response to antidepressant treatment; thus, folate levels may be considered in the evaluation of depressed patients who do not respond to antidepressant treatment. Daily use of folic acid (500 μg) can greatly improve the therapeutic effects of fluoxetine, probably by decreasing levels of homocysteine [69]. It seems that higher levels of folic acid were required in men to optimally decrease folic acid levels.

The chemotherapeutic drug methotrexate interferes with folate metabolism and leads to toxicity; thus, folate supplementation may reduce methotrexate's efficacy during cancer treatment [70]. However, supplementation with folate (1 mg d^{-1}) has been found to have hepatoprotective effects in patients using methotrexate to treat rheumatoid arthritis (RA). These patients required slightly higher doses of the drug but had lower liver enzymes [71]. Folate has also been reported to reduce the effectiveness of several anticonvulsants, potentially leading to seizures [70].

In summary, it is useful to check folate levels in depressed patients. Given the safety profile of folate, a therapeutic trial using physiologic doses may be an option for the CAM practitioner.

40.3.2.4 **Inositol hexaphosphate (IP6)**

An abundant component of plant seeds, inositol is an isomer of glucose that is a precursor in the phosphatidylinositol cycle and a source of two second messengers: diacylglycerol and inositol triphosphate, which may be used for cancer treatment [72]. Animal studies have reported that inositol is effective in relieving symptoms of depression [73]. The antidepressant effect of inositol may involve serotonin receptors and acetylcholine mechanisms [74]. Thus, it is possible that the effects of reuptake antidepressant drugs and the effects of inositol may have a common pathway [75]. Inositol (12 g) was found to be more effective than placebo at week 4 in a double-blind study of 29 patients [76], but other studies have shown little or no benefit. A recent study by Taylor et al. failed to report clear therapeutic benefits in four short-term trials of double-blind design that included a total of 141 patients. These trials showed that patients had good tolerability to inositol [77]. Sodium-IP6 given to 35 patients at a dose of 8.8 g d^{-1} in divided doses for several months resulted in no apparent toxicity [78].

40.3.2.5 **Melatonin**

Melatonin (*N*-acetyl-5-methoxytryptamine), the main secretory product of the pineal gland in the brain, is known to have powerful antioxidant effects and is typically

used to coordinate circadian rhythms in people with insomnia and jet lag. It has also been utilized in the treatment of cancer. Low melatonin levels have been observed in bulimia, neuralgia, and in women with fibromyalgia. The time of the nocturnal melatonin peak secretion was significantly delayed in depressive subjects compared to healthy controls [79], although both groups showed no significant difference in the mean level of melatonin. Interestingly, in patients with major depression, positive response to antidepressants correlated with an increase in their melatonin profiles, but only patients suffering from delayed sleep phase syndrome were successfully treated with melatonin [80].

A reasonable dose of melatonin may be 0.5–5 mg, 20 min before bed. Typical dosages for cancer treatment are often in the 20 mg range [81]. Although side effects are rare, melatonin should be given at a time of day consistent with the sleep-wake cycle (20 min before bedtime). A potential concern in the use of melatonin is that elevated melatonin levels have been associated with exacerbations of nocturnal asthma [82].

40.3.2.6 **S-Adenyosyl-L-methionine (SAMe)**

SAMe is a naturally occurring molecule derived from L-methionine, which acts as a methyl donor and is involved in the synthesis of various neurotransmitters in the brain [83]. This molecule has been found to be safe and effective in the treatment of mild and moderate depression [83, 84]. In a meta-analysis of 47 studies of people with mild-to-moderate depression, SAMe produced a significant improvement in the HAMD score. SAMe treatment was significantly better than placebo and worked as well as conventional drug therapy [85].

One uncontrolled trial administered SAMe in doses of 800 to 3600 mg d^{-1} for a period of 10 weeks in 13 depressed patients with Parkinson's disease; 11 patients completed the study, and 10 had at least a 50% improvement in HAMD. Only one patient did not improve, two patients terminated participation in the study prematurely because of increased anxiety, one patient experienced mild nausea, and another two patients developed mild diarrhea, which resolved spontaneously.

Because oral SAMe may cause nausea, a incremental regimen has been suggested, with a starting dose of 200 mg twice daily for the first day, which is increased to 400 mg twice daily on day 3, then to 400 mg three times daily on day 10, and finally to the full dose of 400 mg four times daily [102]. Little research has been done using SAMe to treat severe depression, so it is unknown whether SAMe would have the same benefits as seen in mild-to-moderate depression.

40.3.2.7 **Selenium**

Selenium is a mineral known for its capacity as an antioxidant, as a cofactor for glutathione peroxidase. Selenium also helps in the conversion of thyroxine to triiodothyronine and can modulate immune function. It has been shown that selenium deficiency encourages depressed mood. Conversely, high dietary or supplementary selenium has been shown to improve mood [86]. Research has consistently reported that low selenium status was associated with significantly increased incidence of depression, anxiety, confusion, and hostility [87]. Even more,

when alcoholism and depression occur together in an individual, there is an increased risk for suicide.

Given the propensity for low selenium status in alcoholic patients and the relationship between selenium levels and mood disorder, selenium supplementation is warranted in an attempt to ameliorate the untoward comorbid psychological and physical profile of patients with alcohol abuse or dependence and may also be of value even in the nonalcoholic depressed individual.

Large doses may cause brittle nails, and one fatality has been reported after the accidental ingestion of 31 mg. Overall, selenium is historically quite safe when taken in prescribed doses, and in high-selenium areas of the country, intake as high as 724 μg d^{-1} was considered safe [88, 89].

40.3.2.8 L-Tryptophan and 5-Hydroxytryptophan (5-HTP)

Tryptophan is a well known amino acid precursor of serotonin (5-hydroxytryptamine). Plasma tryptophan also has antioxidant activity [90]. Research shows that tryptophan is significantly lower in major depressed subjects than in normal controls [91]. Low serum levels of 5-hydroxytryptophan may increase the risk of a suicide attempts in patients who are depressed.

As SSRIs are known to block the reuptake of serotonin, their desired therapeutic effect is through enhancing levels of serotonin in the brain. Supplementing with tryptophan and 5-HTP allows the body to convert more of these amino acids to tryptophan. Some CAM practitioner believe that using tryptophan or 5-HTP is a better method of a achieving the same goal, for it allows the body to have more control over this process, which may mitigate side effects that contribute to the side-effect profile of SSRIs.

When considering whether to use tryptophan or 5-HTP, 5-HTP would probably the better supplement choice. Also known to help in depression [92], 5-HTP has been shown to be more effective at crossing the blood–brain barrier, and oral dosing results in greater conversion to serotonin than dosing with tryptophan (70% vs. 3%, respectively) [102].

When considering serotonin abnormalities in a depressed patient from a naturopathic standpoint, it is important to consider the role and health of the digestive tract. Evidence linking digestive dysfunction, abnormal serotonin levels, and psychiatric illness is emerging. One study demonstrated that 20% of patients with functional bowel disorders also have psychiatric comorbidities [93]. Effectively treating digestive dysfunction may rebalance tryptophan and serotonin levels, thus working to alleviate depressive illness. The naturopathic notion of 'treating the gut' may be of use in treating primary mechanisms of depression.

When dosed accordingly, tryptophan appears to be quite safe and effective. The possibility of eosinophilia myalgia syndrome almost 15 years ago caused concern in the United States after a few individuals fell ill after consuming contaminated batches of the supplement [94]. Probably more salient would be words of caution about 'serotonin syndrome', which is a situation in which SSRI and natural therapies known to increase serotonin levels are used in combination. This syndrome can be characterized by severe agitation, nausea, and confusion. However, with careful

dosing of SSRI drugs and tryptophan, supplementation may provide a side-effect free and useful integrative approach to depression. A randomized controlled trial of 8-week treatment with 20 mg of fluoxetine in combination with 2 g of tryptophan daily in 30 patients with major depression found that this combined treatment appeared to be a safe and that it had both a rapid antidepressant effect and a protective effect on slow-wave sleep, with no need for monitoring of drug levels [95].

In patients who do not require first-line pharmaceutical therapy (see Section 4.1), it may be best for the CAM healthcare provider to choose a prescription-grade high-quality tryptophan or 5-HTP. Since more research is needed to optimize dosing schedule and amounts, it may be best to start with 500 mg d^{-1} of tryptophan and work up to a dose of 2 g d^{-1} if needed. Doses of 5-HTP can start at 100 mg three times a day and work up to 200 mg three times a day. At this time it is not known whether 5-HTP can be dosed with fluoxetine, and any attempt to use them in an integrative fashion should begin cautiously. One recent meta-analysis of tryptophan and 5-HTP studies found few of high quality and merit. Out of 108 studies, only two studies (one of 5-HT and one of L-tryptophan) with a total of 64 patients met sufficient quality criteria to be included. These studies suggested that 5-HTP and L-tryptophan are better than placebo at alleviating depression [96]. But more quality research on a larger number of individuals is clearly needed.

40.3.2.9 **Vitamin E**

Depression has been associated with decreased antioxidant capacity and increased lipid peroxidation [97]. In a study evaluating 26 healthy volunteers and 42 depressed patients, patients with major depression had significantly lower serum vitamin E concentrations than healthy controls [98]. Given the relative safety of vitamin E supplementation and the possible benefits to both the cardiovascular system and to decreasing oxidative damage, it is reasonable to supplement patients having major depression with 400 IU of vitamin E d^{-1}.

40.3.2.10 **Zinc**

Known as a mineral cofactor, zinc is responsible for wound healing and immune- and nervous-system modulation. It has been postulated that zinc may act as an antagonist of the NMDA glutamate receptor [99]. In general, unipolar depression is connected with low blood zinc levels that are known to increase during antidepressant therapy [100]. One double blind placebo-controlled pilot study of zinc supplementation during antidepressant therapy was conducted with patients who met DSM IV criteria for major depression. A total of 14 patients received either zinc supplementation at 25 mg zinc d^{-1} or placebo and were concomitantly treated with standard antidepressants [101]. Zinc supplementation significantly reduced both Hamilton Depression and Beck Inventory scores after 6- and 12-week supplementation when compared with placebo treatment. Due to theoretical depletion of copper by zinc treatment, long-term supplementation (greater than two months) with zinc should be balanced with copper supplementation.

40.4
Important Lifestyle Factors Targeted by CAM in Depressed Persons

40.4.1
Diet and the Digestive System

Nutrient deficiencies are common in depressed patients. Impaired digestive function can often claim significant responsibility for these deficiencies. Making matters worse, the Standard American Diet (SAD) fails to provide the high-quality nutrients necessary for metabolic processes (such as folic acid, B vitamins), for antioxidant protection (such as vitamins E and C), and for providing the necessary amino acid precursors for neurotransmitters (such as the amino acid tryptophan). High quality and varied types of vegetables and fruits, as well as adequate fiber and protein sources, are crucial to the physical and mental health of any individual. It seems reasonable to assume that systems under stress, like that of the depressed patient, would require these even more; but these assumptions have not been fully characterized or studied. Related to this, the patient must also attempt to eat in a quiet environment and learn to chew food well for good digestion. Given that a large percentage of adults skip meals or eat in the car, this alone can be quite a lofty goal for the depression sufferer and the CAM practitioner.

40.4.2
Tobacco, Alcohol, and Recreational Drugs

Comorbid substance abuse is detailed addressed in Chapter 13 of this book. Cigarette smoking also leads to a relative deficiency in vitamin C [102]. As lipid oxidation is increased in depressive illness [97], this becomes a crucial health issue. Depressive symptoms, smoking, and sedentary behavior are independent predictors of mortality. Results indicate that smoking and/or sedentary behavior may partially mediate the relation between depressive symptoms and mortality [103].

Alcohol can lead to increased adrenal cortisol and is known to disrupt sleep architecture. Chronic alcohol ingestion also depletes a number of vitamins and nutrient cofactors, as well as causing precipitous changes in blood sugar. Recreational drug use (e.g., of cannabis) is known to increase the occurrence of depressive symptoms [104].

40.4.3
Sleep

Regular sleep is of paramount importance to good health. Given the poorly characterized yet global effects of circadian rhythm on overall hormonal regulation, it is reasonable to consider instituting lifestyle changes that support circadian rhythm function. Changing to an earlier bedtime, implementing support for regular sleep patterns (minimizing nighttime light, eating a diet adequate in protein, maintaining a reasonable eating schedule, balancing blood sugar, supplementing

with melatonin, etc.), and assuring exposure to morning sunlight may have far-reaching effects on depressive illness. More specifically, certain types of depression may be even better amenable to certain therapies. For instance, one observational study noted that exposure to morning sunlight, a mainstay for treating seasonal affective disorder, can have therapeutic effects in bipolar depression but not in unipolar illness [105]. See Section 3.1.2 ■for more information about sleep and depression.

40.4.4 Exercise

Throughout history, many societies, ancient and modern, have used exercise as a means of preventing disease and promoting health and well-being [106]. Exercise may be the most beneficial form of depression therapy [102]. Known to elevate mood [107], exercise is also known to balance blood sugar, raise levels of good cholesterol, and improve cardiac function. There is ample evidence that exercise is beneficial to mental health, for it reduces anxiety, depression, and negative mood and improves self-esteem and cognitive functioning [106]. In a randomized controlled trial, 156 adults with major depression were assigned to a 4-month course of aerobic exercise, sertraline therapy, or a combination of exercise and sertraline. After four months patients in all three groups exhibited significant improvement; But after 10 months, subjects in the exercise group had significantly lower relapse rates ($p = 0.01$) than subjects in the medication group. Additionally, exercising on one's own during the follow-up period was associated with a reduced probability of depression diagnosis at the end of that period ($p = 0.0009$) [108]. In another randomized controlled trial, 156 patients at least 50 years old were given exercise or antidepressant medications. That study found that initially, a quicker improvement was found in the antidepressant group. But after 16 weeks of treatment, exercise was equally effective in reducing depression among older patients with major depression [109]. Finally, in a 2-year follow up study of post-MI patients with depression, those who performed regular exercise were shown to have less than half the risk of fatal cardiac events than patients who did not [110].

40.4.5 Other Lifestyle Factors and Further Considerations

Low socioeconomic status and social isolation can contribute to depressed mood and should be addressed for solutions when possible.

The nature-cure notion of getting enough sunlight also seems to be playing out in the medical literature as more information regarding the role of vitamin D and mood is emerging. Since research demonstrates that dosages of 100 μg vitamin D (4000 IU d^{-1}) in depressed patients tend to improve well-being [111], it makes sense for the CAM practitioner to ensure that patients who tend to get inadequate amounts of sunlight begin to get outside and enjoy the sun. Of course, those at higher risk

for melanoma and other skin cancer should be more cautious and may consider using a vitamin D supplement.

In summary, modification of the above lifestyle factors plays a fundamental role in addressing the symptoms and underlying presumed causative aspects of depressed mood. It is important for the CAM practitioner to ferret all these out and to spend time with the patient devising an individualized plan to positively adjust these factors. It is often helpful to keep in mind several factors when implementing long-term healthful lifestyle changes, including patient education to clarify the purpose of the suggested treatment, being realistic as to what factors the patient is willing and able to change at that time, and meeting the patient where they are. As the art of CAM medicine dictates, it is up to the individual practitioner to use his or her knowledge of treatment modalities, clinical experience, intuition, and consideration of patient preferences when deciding on which options would be most efficacious for the individual patient.

Other CAM therapies relevant to the treatment of major depression include psychological support, such as the emotional freedom technique (EFT) [112, 113], neurolinguistic programming (NLP) [114, 115], and eye movement desensitization and reprocessing (EMDR); acupuncture [116, 117]; and energetic healing therapy/Reiki [118]. Biofeedback, guided imagery, and massage therapy have also been reported to transiently help with pain and anxiety [119–123].

40.5 Conclusions

Depression is a multifactorial disease that is governed by a complex system modulated by lifestyle, dietary, psychological, spiritual, nutritional, and physiological aspects. Although the term 'depression' is used as a diagnosis, the CAM practitioner perceives this condition to be vastly different for each patient and a result, the CAM practitioner tries to understand the multiplicity of factors that can be contributing to the patient's condition and then applies that knowledge in a synergistic way most in line with the probable causes of illness. In this way, the CAM clinician tries a double approach: to help the patient's immediate mood problems and then, more importantly, to give long-term healing its best chance of occurring by ministering to the underlying causes of depression. Unfortunately, a large portion of the public uses DS without consulting a CAM or non-CAM practitioner.

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