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Update and Critique of Natural Remedies as Antidepressant Treatments

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SYNOPSIS

The popularity of natural or “alternative” remedies to treat medical and psychiatric disorders has accelerated dramatically over the past decade, in the United States and worldwide. This article reviews the evidence for clinical efficacy, active ingredients, mechanisms of action, recommended dosages, and toxicities of the three best-studied putative natural antidepressants, St. John's Wort (hypericum), S-adenosyl methionine, and the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid. Despite growing evidence for efficacy and safety, more comprehensive studies are required before these remedies can be recommended as safe and effective alternatives or adjuncts to conventional psychotropic agents. There are limited data regarding safety in pregnancy and during lactation, and caution is therefore recommended in women who are pregnant or breastfeeding.

Keywords

Omega-3; EPA; DHA; St. John's Wort; hypericum; S-adenosyl methionine; SAMe; eicosapentanoic; docosahexanoic; depression

Natural or “alternative” remedies have been routinely used in Asia and Europe for centuries [1], and the popularity of these medications in the United States and worldwide has accelerated dramatically over the past decade. Increasing numbers of patients now are asking their doctors whether they might benefit from natural treatments, and many patients see a variety of practitioners in addition to physicians, including herbalists, naturopaths, and other healers. Because natural remedies are readily available over the counter, many individuals are choosing to self-medicate without professional supervision.

The National Institutes of Health has recognized that up to 25% of people in the United States seek and obtain alternative treatments [2], and Eisenberg and colleagues [3] found that 33% of patients at Boston's Beth Israel Medical Center use some form of complementary and alternative medicine. In 1990 there were more visits to alternative treatment practitioners nationwide than to primary care physicians [3]. The World Health Organization reported that

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that more than 70% of the world's population uses nonconventional medicine [4]. Growing numbers of academic investigators are performing clinical and basic research on these agents, and medical schools and residency training programs are starting to include complementary and alternative medicine in their curricula. Most physicians, however, still feel relatively unequipped to advise patients who ask about alternative treatments, and many practitioners remain highly skeptical of their potential value.

The benefits and liabilities of herbal remedies and other natural treatments still are largely unclear. Medical research has historically overlooked this area, and nutraceutical companies do not routinely fund studies on these medications [5]. Perhaps the most unfortunate—and dangerous—public misconception about these alternative medications is the belief that, just because something is “natural,” it is automatically safe. Although historically the relatively few reports of serious adverse effects from these medications have been a large part of their appeal [1], there increasingly have been cases of individuals who have had toxic reactions from these agents, whether or not they exceeded the recommended dosage [1], [6]. Likewise, there are limited data regarding the safety and efficacy of combining alternative medications with conventional ones, but reports of adverse interactions have begun to emerge for some substances.

Natural medications, with the exception of homeopathic remedies, generally are not regulated by the US Food and Drug Administration (FDA) [5], [7]. Consequently, optimal doses for these medications are poorly established, as are the active ingredients, contraindications, drug–drug interactions, and potential toxicities. Another consequence of the lack of regulation is that preparations made by different companies vary in regard to form, quality, or purity of the medication—and hence in effectiveness.

Although natural medications are available for most physical and medical problems, there are relatively fewer ones for psychiatric disorders, and these treatments are mainly limited to mood and anxiety symptoms and senescent cognitive decline. This article reviews three of the best-studied natural medications for mood disorders, St. John's Wort (hypericum), S-adenosyl methionine (SAME), and the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

St. John's Wort

Hypericum is an extract of the flower of St. John's Wort (*Hypericum perforatum* L.) that has been used for the treatment of depression for centuries [1]. Physicians in Europe have long considered hypericum effective for treating mild-to-moderate depression. In the past decade, interest in St. John's Wort has increased dramatically in the United States and worldwide, and today it is one of the biggest-selling natural remedies on the market.

Mechanisms of Action

The mechanism of action of hypericum is not fully understood. The extract from St. John's Wort contains polycyclic phenols, hypericin and pseudohypericin, which are among the presumed active components; other compounds include flavonoids (hyperoside, quercetin, isoquercitrin, rutin), kaempferol, luteolin, biapigenin, and hyperforin [8], [9], [10]. Hypericin, believed to be one of the main active components in hypericum, decreases serotonin receptor density [11]. Because hypericin does not cross the blood–brain barrier, one proposed mechanism of action for hypericin is the inhibition of monocyte cytokine production of interleukin 6 and 1β , resulting in a decrease in corticotropin releasing hormone and thus dampening production of cortisol [12]. Hypericin also may inhibit reuptake of serotonin, norepinephrine, and dopamine [11] and may thus result in reduced expression of beta

adrenoreceptors and increased density of serotonin (5-HT_{2A} and 5-HT_{1A}) receptors [13]. Hypericin also may have affinity for γ -aminobutyric acid receptors.

More recent investigations have implicated hyperforin as a possible active ingredient [14]. Laakmann and colleagues [15] performed a randomized, double-blind, placebo-controlled 6-week study of two different extracts of hypericum, on 147 patients. The two extracts contained 0.5% and 5% hyperforin, respectively. Patients who received the hypericum extract with 5% hyperforin showed greater improvement in mean Hamilton Depression Scale (HAM-D) scores than the group receiving the 0.5% hyperforin extract, and the latter group showed only slightly greater improvement than the placebo group.

Various mechanisms of antidepressant action for hyperforin have been proposed, including serotonin reuptake inhibition and norepinephrine and acetylcholine reuptake inhibition. Some studies suggest inhibition of serotonin, dopamine, norepinephrine, γ -aminobutyric acid, and L-glutamate [16], although serotonergic mechanisms probably are most important. Other mechanisms have been proposed also, including reduced expression of cortical beta-adrenoceptors and 5-HT₂ receptors and synaptosomal release similar to that caused by reserpine [14].

Other components of hypericum, including the flavonoids, are irreversible monoamine oxidase-A inhibitors, but the concentration of these compounds in the extract are so small that they are unlikely to be involved in the antidepressant mechanism [17].

Most commercially available St. John's Wort preparations are standardized either to hypericin or hyperforin. Because there are several different preparations of the medication, the amount of other active ingredients may vary with different preparations, and there are no published head-to-head trials with different brands of Hypericum.

Efficacy

In general, hypericum has been reported to have efficacy greater than placebo and equal to active controls. There are approximately 35-40 published trials, including 26 placebo-controlled studies and 14 with a standard antidepressant as the active comparator [18]. Most studies have been conducted in Europe, usually with patients already in clinical care in general practice settings [1]. Results in such studies may be more predictive of effectiveness and acceptability in clinical practice but may differ widely from results in a controlled research setting. For example, the European studies generally report little about the methods of recruitment, whether consecutive patients were recruited, and what, if any, exclusion criteria were applied. Patient groups in many European studies of hypericum were not limited to major depression and included other diagnoses [1], [14].

In clinical trials hypericum has been compared with low doses of both imipramine and maprotiline [19], [20], [21], [22]. Doses of imipramine and maprotiline used in European clinical practice tend to be lower than those considered adequate by psychopharmacologists in the United States. In these clinical trials, the typical dose of imipramine or maprotiline is 75 mg/d. Despite the inadequate doses of active controls, the response rates in these trials seemed comparable to those in studies that use higher doses of tricyclic antidepressant agents (TCAs) (eg, imipramine >150 mg/d). The lack of a placebo control makes it difficult to interpret the results, but hypericum seemed to be at least as effective as low doses of imipramine and maprotiline. In these studies, response rates for hypericum ranged from 35.3% to 81.8%, and response for TCAs ranged from 41.2% to 77.8%.

A meta-analysis by Nierenberg [23] examined four studies comprising a heterogeneous group of depressive conditions, in which hypericum, 300 mg three times per day, was judged to be

effective in 79 of 120 subjects (65.8%), whereas placebo was considered effective in only 36 of 125 subjects (28.8%; chi square 32.24; $P < .0001$). The placebo response rate seemed comparable to that observed in many outpatient studies of antidepressants conducted in the United States.

A meta-analysis by Linde and colleagues [24] examined 15 trials comparing Hypericum with placebo and eight trials comparing Hypericum with TCAs in 1757 patients who had mild-to-moderate depression. In six trials that used single preparations of Hypericum (containing only St. John's Wort), hypericum yielded greater response rates than placebo (55.1% for Hypericum versus 22.3% for placebo) and comparable response rates to tricyclic antidepressants (63.9% for Hypericum versus 58.5% for tricyclic antidepressants). In two trials that used combination preparations of Hypericum (containing St. John's Wort and other herbal medications such as Kava), Hypericum was found to be more effective than TCAs (67.7% versus 50%). A meta-analysis by Voltz [25] suggested that Hypericum may not be effective for acute treatment of severely depressed patients.

In the 2000s, approximately 10 notable studies by North American, European, and South American investigators have been published. Many of these studies are distinguished by their large-scale, randomized, double-blind design and/or by comparing St. John's Wort with newer antidepressants, particularly the selective serotonin reuptake inhibitors (SSRIs), as well as with placebo.

In a 6-week trial with 375 patients, Lecrubier and colleagues [26] found that St. John's Wort, 900 mg/d, was significantly more effective than placebo, especially in patients who had higher baseline HAM-D scores. In an 8-week trial with 200 depressed subjects, Shelton and colleagues [27] found that St. John's Wort, 900 to 1200 mg/d, was no more effective than placebo in the full intent-to-treat analysis, although among completers the remission rates were significantly higher with St. John's Wort than with placebo.

Brenner and colleagues [28] compared St. John's Wort, 900 mg/d, versus sertraline 75, mg/d, in 30 depressed subjects for 6 weeks. St. John's Wort yielded a 47% response rate and sertraline a 40% response rate. The difference was not statistically significant. Gastpar and colleagues [29] also compared St. John's Wort, 612 mg/d, against sertraline, 50 mg/d, in 241 depressed subjects for 12 weeks, with 161 subjects receiving an additional 12 weeks of treatment for a total treatment period of 6 months. By the first 12 weeks, Hypericum was found to yield a response rate comparable to sertraline, and this response was maintained in subjects who continued for the full 6 months. van Gurp and colleagues [30] compared St. John's Wort, 900 to 1800 mg/d, with sertraline, 50 to 100 mg/d, in 12 community-based primary care offices. Eighty-seven depressed subjects were treated for 12 weeks. No significant differences in mean HAM-D scores were found, and St. John's Wort resulted in significantly fewer adverse events.

Schrader [31] compared St. John's Wort, 500 mg/d, with fluoxetine, 20 mg/d, for 6 weeks in 240 depressed subjects. St. John's Wort yielded a 60% response rate and fluoxetine a 40% response rate. Results barely reached significance in favor of St. John's Wort. The authors noted that St. John's Wort had a more favorable adverse-effects profile. Only 8% of subjects receiving St. John's Wort reported adverse events compared with 23% receiving fluoxetine. Behnke and colleagues [32] compared St. John's Wort with fluoxetine in 70 mildly to moderately depressed subjects for 6 weeks. They found HAM-D score decreases of 50% for St. John's Wort and 58% for fluoxetine, with the efficacy of St. John's Wort approximately 80% of that of fluoxetine on the HAM-D and the von Zerssen Depression scales.

The Hypericum Depression Study Group [33] compared St. John's Wort at doses of 900 to 1500 mg/d versus sertraline, 50 to 100 mg/d, or placebo for 8 weeks in 340 depressed subjects. St. John's Wort and sertraline both yielded a response rate of approximately 24%; the response

rate for placebo was 32%. This report, along with that of Shelton and colleagues [27], resulted in a great deal of media attention during 2002, and St. John's Wort sales worldwide dropped temporarily in the immediate aftermath [5].

Fava and colleagues [34] at the Massachusetts General Hospital (MGH) conducted a study similar to the Hypericum Group's, comparing St. John's Wort, 900 mg/d, with fluoxetine, 20 mg/d, versus placebo for 12 weeks. The study was powered for 180 subjects, but the sponsor closed the study prematurely because of the media hysteria over the previously mentioned negative studies, which were published while the MGH study was in progress. Consequently, only 135 subjects were recruited. The results showed a trend toward significance for St. John's Wort against placebo with regard to decrease in HAM-D scores and a significant advantage for St. John's Wort against fluoxetine. Remission rates were 38% for St. John's Wort, 30% for fluoxetine, and 21% for placebo, but these differences did not reach significance. In view of the placebo response rate, which was consistent with the literature, the authors concluded that the observed results were "real" and suggested that if the full complement of 180 subjects had been recruited, both St. John's Wort and fluoxetine would have beaten placebo by a statistically significant margin.

Moreno and colleagues [35] compared hypericum, 900 mg/d, with fluoxetine, 20 mg/d, or placebo in 72 depressed subjects. After 8 weeks, the authors found that hypericum yielded a remission rate of 12%, significantly lower than that of fluoxetine (34.6%) and placebo (45%).

How should these recent studies be interpreted in the context of the previous literature? A recent Cochrane review declared similar response rates overall for St. John's Wort, SSRIs, and TCAs but cautioned about the "inconsistent and confusing" nature of the data [18]. In comparisons between St. John's Wort and placebo, the results tended to favor St. John's Wort but more so in cases where there was not a strict diagnosis of major depressive disorder. Trials with strictly diagnosed depression according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM) criteria showed less robust results [18]. More studies are necessary to clarify some of the questions about efficacy that the aforementioned studies have raised.

Safety and Tolerability

In the past few years, increasing numbers of adverse drug–drug interactions between St. John's Wort and other medications have been reported in the literature. These interactions are thought to occur largely through the liver enzyme CYP-450-3A4 and have resulted in decreased activity of several drugs, including warfarin, cyclosporin, oral contraceptives, theophylline, phenprocoumon, digoxin, indinavir, and irinotecan [36], [37], [38], [39], [40]. Extreme caution, therefore, is required with HIV-positive patients who take protease inhibitors, cancer patients receiving chemotherapy, and transplant recipients who take immunosuppressive drugs. It also is recommended that St. John's Wort not be combined with SSRIs, because anecdotes of "serotonin syndrome" have been reported, presumably related to St. John's Wort's monoamine oxidase inhibitor activity [41].

When St. John's Wort is used as monotherapy, adverse events are relatively uncommon and mild [42]. Patients have complained of dry mouth, dizziness, constipation, other gastrointestinal symptoms, and confusion [1], [42]. Woelk and colleagues [43] followed 3250 patients treated with hypericum by 633 physicians in routine clinical practice and found that only 2.4% of patients mentioned side effects of gastrointestinal symptoms and allergic reactions. Only 1.5% of patients stopped taking the drug because of these side effects. So far, there seem to be no published reports assessing the effects of an hypericum overdose.

Phototoxicity has long been associated with hypericum in grazing animals and has been reported, albeit rarely, in humans [44]. Brockmoller and colleagues [45] found that doses of hypericum as high as 1800 mg caused minor increases in sensitivity to UV light in humans but no phototoxicity. Siegers and colleagues [46] have recommended that patients who take an overdose of hypericum should be isolated from UV radiation for 7 days, but this caution may not necessarily apply to patients receiving regular doses. As a general precaution, the author and colleagues recommend that patients who take St. John's Wort use sunscreen and other protection when spending large amounts of time in the sun.

At least 17 cases of psychosis resulting from St. John's Wort have been reported, of which 12 comprised mania or hypomania [47]. Bipolar patients therefore should be advised to use St. John's Wort only with a concurrent mood stabilizer.

Recommendations and Special Considerations for Women who are Pregnant or Breastfeeding

Hypericum has been shown to be more effective than placebo and equal to low-dose TCAs in most controlled trials but has had less impressive results against the SSRIs and placebo in the more recent studies, perhaps in part because of the recruitment of more severely and/or chronically depressed patient samples [14].

Recommended doses of St. John's Wort based on the literature fall between 900 mg and 1800 mg/d, usually divided on a twice- or thrice-daily basis. St. John's Wort seems to have a relatively benign side-effect profile, although, given the risk of interactions, care needs to be taken with patients taking multiple medications. Likewise, in view of the risk of cycling, caution should be exercised in patients who have bipolar disorder.

The literature as a whole suggests that St. John's Wort may be less effective in cases of more severe and/or more chronic depression, and people who have milder forms of depression therefore may be the best candidates for St. John's Wort. A collaborative study of St. John's Wort for minor depression at MGH and Cedars-Sinai Medical Center has recently been completed, and data analysis is currently underway. Hypericum needs to be studied further in depressed subjects who have rigorously diagnosed DSM-IV major depression, using placebo and active controls for acute treatment periods of at least 8 to 12 weeks. Longer-term continuation treatment also merits investigation, and systematic tracking of side effects needs to be further developed.

Little is known about toxic effects that hypericum may have during pregnancy and breastfeeding. A systematic literature review [48] found that in-utero exposure to SJW in animals may be associated with low birth weight but no adverse effects on cognitive development; breastfeeding while on SJW was associated with colic and drowsiness or lethargy [48]. Given SJW's CYP450 induction, concerns were raised over its potential interference with other medications administered during pregnancy or lactation [48]. One small prospective study found no significant differences in fetal malformations in women exposed to SJW during pregnancy, compared to pregnant women on other antidepressants and pregnant women with no teratogen exposure [49]. Studies examining hyperforin and hypericin levels in breast milk have suggested safety for children and mothers [50],[51] and one small prospective study suggests no increase in adverse events in children exposed to SJW in mother's milk, though cases of lethargy and drowsiness were reported [52]. The data, however, are scanty and long-term studies of safety are required [53]. In the absence of safety data, it is recommended that women who are pregnant or intend to become pregnant avoid St. John's wort.

S-adenosyl methionine

SAMe ([Box 1](#)) is a methyl donor in the brain, involved in the pathways for synthesis of hormones, neurotransmitters, nucleic acids, proteins, and phospholipids [54]. Of particular interest is its activity as an intermediate in the synthesis of norepinephrine, dopamine, and serotonin [54], which suggested its potential role in mood regulation. Widely prescribed in Europe for decades, SAMe gained popularity in the United States following its release as an over-the-counter dietary supplement in 1998–1999. It is considered a potential treatment for major depression as well as for a number of other medical conditions [54].

Mechanisms of Action

SAMe is synthesized from the amino acid L-methionine through the one-carbon cycle, a metabolic pathway involving the vitamins folate and B12 [54]. Deficiencies of both these vitamins have long been associated with depression. For example, 10% to 30% of depressed patients may have low folate, and these patients may respond less well to antidepressants [55]. Administration of folate augmentation to partial responders to antidepressants has yielded encouraging results [56], [57]. Vitamin B12 is converted to methylcobalamin, which also is involved in the synthesis of various central nervous system neurotransmitters. B12 deficiency may result in an earlier age of onset of depression [58]. The final pathway of these vitamin deficiencies may be reduced SAMe, leading to diminished synthesis of vital neurotransmitters. The replenishment of folate and B12 may in turn result in increased SAMe and neurotransmitter synthesis. Indeed, low SAMe levels have been found in the cerebrospinal fluid of depressed individuals [59], and higher plasma SAMe levels have been associated with improvement in depressive symptoms [60]. The enzyme methionine adenosine transferase, necessary for the manufacture of SAMe, has decreased activity in depressed schizophrenic patients but increased activity in manic patients [61], [62], [63]. If correction of B-vitamin deficiencies can increase SAMe levels and hence alleviate depressive symptoms, it is reasonable to postulate that direct administration of SAMe also could reverse a depressed state.

Efficacy

There are approximately 45 published randomized clinical trials of SAMe for treatment of depression, of which at least 8 used an active comparator [54], [64], [65], [66]. SAMe demonstrated superiority to placebo in six of eight placebo-controlled studies with sample sizes ranging from 40 to 100 individuals and equivalency to placebo in the other two studies [54], [65], [66]. In six of eight comparison studies with TCAs, SAMe was equivalent in efficacy to TCAs and was more effective than imipramine in one study [54], [65], [66]. Doses of SAMe in these studies ranged from 200 to 1600 mg/d administered orally, intramuscularly, or intravenously [54], [65], [66].

Overall, trials of oral SAMe suggest efficacy comparable to TCAs and superiority to placebo at doses between 200 and 1600 mg/d [64], [65], [66]. Although some early studies yielded equivocal results because of problems with dissolution and stability of early oral SAMe preparations [54], [65], [66], current oral SAMe preparations are tosylated and are more stable and thus are more suitable for research use. As yet there are no published reports comparing SAMe against newer antidepressants such as SSRIs, but such studies are in progress.

SAMe may have a relatively faster onset of action than conventional antidepressants [54], [65], [66]. In one study, some patients improved within a few days, and most did so within 2 weeks [67]. Likewise, two studies showed that the combination of SAMe and a low-dose TCA resulted in earlier onset of action than a TCA alone [68], [69].

A recent study by Alpert and colleagues [70] examined the efficacy of SAME as an adjunctive treatment for partial and nonresponders to SSRIs. Thirty subjects who had residual depression despite SSRI or venlafaxine treatment received a 6-week course of SAME, 800 to 1600 mg. Response and remission rates with SAME augmentation were 50% and 43%, respectively, and the treatment was well tolerated. The results suggest a possible role for SAME as an augmenting agent in cases of partial or nonresponse to SSRIs. A placebo controlled follow-up augmentation study comparing SAME against placebo in SSRI nonresponders has recently been completed in our group, and analysis of these findings is in progress.

Other reports suggest that SAME is effective for dementia-related cognitive deficits, depression in patients who have Parkinson's disease or other medical illness, psychological distress during the puerperium, and opioid and alcohol detoxification [66].

Safety and Tolerability

SAME is well tolerated and relatively free of adverse effects. There is no apparent hepatotoxicity or anticholinergic effects. Side effects include mild insomnia, lack of appetite, constipation, nausea, dry mouth, sweating, dizziness, and nervousness [54]. Cases of increased anxiety, mania, or hypomania in bipolar depression have been reported [54], [671], [72], and therefore care must be taken with patients who have a history of bipolar disorder. These patients should be advised not to take SAME unless they are receiving a concurrent mood stabilizer. So far, there seem to be no significant drug–drug interactions between SAME and FDA-registered drugs.

Recommendations and Special Considerations for Women who are Pregnant or Breastfeeding

There is encouraging evidence that SAME is effective for treatment of major depression, both as monotherapy and as an adjunct to FDA-approved antidepressants. Some studies have suggested a faster onset of action for SAME than for conventional antidepressants, and it may accelerate the effect of conventional antidepressants when combined. SAME seems to be well tolerated, with a relatively benign side-effect profile. It may be especially good for patients who are sensitive to antidepressant-related side effects, particularly the elderly and those who have medical comorbidity. There is no apparent toxicity, except for risk of cycling in patients who have bipolar depression. Recommended doses range from 400 to 1600 mg/d [54], [65], [66], although in clinical practice the author and colleagues have observed some individuals who require at least 3000 mg/d for alleviation of depression. More research is needed to determine optimal SAME doses, and head-to-head comparisons with newer antidepressants should help clarify SAME's place in the psychopharmacologic armamentarium.

SAME is relatively expensive, with prices ranging from \$0.75 to \$1.25 for a 400-mg tablet. Because insurance plans do not cover over-the-counter supplements, the out-of-pocket cost can be prohibitive to many patients, particularly those who may require higher doses. Careful shoppers who search the Internet may be able to purchase SAME at more accessible prices, but they should verify the reputation of the seller. With increasing numbers of manufacturers and competition in the marketplace, it is hoped that the price of SAME will drop in the foreseeable future.

As with St. John's wort, there is a lack of data regarding safety during pregnancy and lactation. Some studies have found that pregnancy may result in impaired methylation and lower levels of SAME [73], suggesting a potential benefit from SAME administration in pregnant women. SAME supplementation in pregnant women with intrahepatic cholestasis has been associated with beneficial effects [74]. While SAME appears to be a mostly safe over-the-counter agent—i.e. a chemical that humans already manufacture, with no drug-drug interactions, and

minimal and mild adverse effects—consideration for SAME administration in selected cases may be reasonable [53]. But given the limited data, the pregnant woman is likely better off avoiding SAME, particularly when considering that there are many registered antidepressants with proven track records for safety and efficacy during pregnancy.

Omega-3 fatty acids

During the past century, intake of omega-3 fatty acids in the Western diet has decreased dramatically, while intake of processed foods rich in omega-6—containing vegetable oils has increased. This dietary shift has resulted in a higher physiologic ratio of omega-6:omega-3 fatty acids in Western countries compared with countries with higher fish and omega-3 consumption [75], [76], [77], [78], [79]. The modern Western diet and the additional stresses of twenty-first century life have been postulated to create a baseline proinflammatory state in humans that may contribute to cardiovascular disease and also may play a role in the development of mood disorders [80]. Administration of omega-3 supplements may potentially reverse this proinflammatory state by correcting the omega-6:omega-3 ratio, thus providing beneficial cardiovascular and mood-related effects. Several recent treatment studies have yielded encouraging, albeit preliminary, evidence of clinical efficacy for omega-3 fatty acids as mood-enhancing agents. The two omega-3 fatty acids thought to be relevant to psychiatry are EPA and DHA (Box 2), both of which are found primarily in fish oil. Investigations into their efficacy have examined EPA and DHA separately and in combination with each other.

Mechanisms of Action

How might the omega-3 fatty acids exert their mood-enhancing effect? Proposed mechanisms for the amelioration of depression include an effect on membrane-bound receptors and enzymes involved in the regulation of neurotransmitter signaling, as well as regulation of calcium ion influx through calcium channels [80]. Hamazaki and colleagues [81] found that administration of a combination of EPA and DHA to healthy subjects resulted in a lowering of plasma norepinephrine levels compared with placebo, and the authors proposed that omega-3s could exert their effect by interaction with the catecholamines. Omega-3 fatty acids also may inhibit secretion of inflammatory cytokines, thus leading to decreased corticosteroid release from the adrenal gland and dampening mood-altering effects associated with cortisol [80], [82]. For example, EPA inhibits the synthesis of prostaglandin E₂, thus dampening the synthesis of p-glycoprotein, the latter of which may be involved in antidepressant resistance [82]. In this regard, EPA resembles amitriptyline, which also inhibits p-glycoprotein and is generally considered useful for resistant depression.

Efficacy

Approximately 20 controlled trials and a few open studies with EPA and/or DHA suggest that supplementation with omega-3 fatty acids at doses about five or more times the standard dietary intake in the United States may yield antidepressant and/or mood stabilizing effects. Various meta-analyses of depression studies with omega-3 [83],[84],[85],[86] generally support efficacy of the omega-3, but are limited by mixed samples of augmentation and monotherapy studies, small sample sizes, inclusion of bipolar subjects, and different preparations and doses of omega-3, ranging from 1 to 10 g/day.

Peet and Horrobin [87] conducted a randomized, placebo-controlled, dose-finding study of ethyl-eicosapentaenoate (EPA) as adjunctive therapy for 70 adults who had persistent depression despite treatment with a standard antidepressant. Subjects who received 1 g/d EPA for 12 weeks showed significantly higher response rates (53%) than subjects receiving placebo (29%), with notable improvement of depressed mood, anxiety, sleep disturbance, libido, and suicidality. The 2 g/d group showed little evidence for a drug:placebo difference, and the 4 g/

d group showed a nonsignificant trend toward improvement. These results suggest that there may be an optimal dose of omega-3 that humans require for maximum benefit, and it is possible that an overcorrection of the omega-6:omega-3 ratio with higher omega-3 doses may limit the antidepressant effect of EPA.

Su and colleagues [88] conducted an 8-week, double-blind, placebo-controlled trial comparing adjunctive omega-3 (6.6 g/d) against placebo in 28 depressed patients. Patients in the omega-3 group had a significant decrease in HAM-D scores compared with placebo. In a sample of 20 subjects who had major depressive disorder and were receiving antidepressant therapy, Nemets and colleagues [89] found a statistically significant benefit of adjunctive EPA, 1 g/d, and a clinically important difference in the mean reduction of the 24-item HAM-D scale by the study endpoint at week 4 compared with placebo (12.4 versus 1.6). Frangou and colleagues [90] treated 75 depressed subjects with ethyl-EPA at 1 g/d, 2 g/d, or placebo for 12 weeks. EPA outperformed placebo significantly in both EPA treatment arms, based on HAM-D scores; the higher dose of EPA seemed to confer no added benefit compared with 1 g/d. A recent randomized controlled study by our group examined EPA monotherapy for depression, and found an advantage for EPA compared to placebo, though the study was limited by a smaller than projected sample size [91].

A small study by Silvers [92] suggested that 8 g of “fish oil” was not more effective than 8 g of “olive oil,” but this underpowered study was limited by problems with attrition, dosage, and choice of rating scales. Regarding DHA, one placebo-controlled study with 36 subjects showed lack of efficacy of DHA monotherapy, 2 g/d, for depression [93]. A three-armed dose-finding study of DHA monotherapy [94] demonstrated greater efficacy for DHA doses of 1 g/day compared to 2 g/day and 4 g/day, which, similarly to Peet and Horrobin's study of EPA, suggests a therapeutic window for DHA as well as EPA.

Freeman and colleagues [95] performed a dose-finding trial of omega-3 in 16 women who had postpartum depression. Subjects received 0.5 g/d, 1.4 g/d, or 2.8 g/d. HAM-D scores and the Edinburgh Post Natal Depression Scale both decreased by approximately 50% for all groups, and there seemed to be no dose-response effect. Marangell and colleagues [96] found no preventive effect of postpartum depression with open omega-3 mix (EPA and DHA), 2960 mg/d, in a small sample of pregnant women. A prospective large scale study [97] found no association between fish intake or n-3 intake and risk of post-partum depression.

Omega-3 fatty acids may have efficacy for bipolar as well as unipolar mood disorders. Using high doses of an omega-3 fatty acid mix (6.2 g EPA plus 3.4 g DHA) versus placebo over a 4-month period, Stoll and colleagues [98] found that among 30 patients who had bipolar I or II disorder, a Kaplan-Meier survival analysis revealed a significantly longer duration of remission for those receiving adjunctive omega-3 fatty acid mix versus placebo along with their current mood stabilizing regimen.

Keck and colleagues [99] were unable to replicate Stoll and colleagues' results in a larger-scale study. In their double-blind, placebo-controlled trial of adjunctive EPA, 6 g/d, for 4 months in patients who had bipolar depression (n = 57) or rapid cycling (n = 59), EPA did not separate from placebo. Systematic reviews of bipolar studies suggested that most of the observed benefit in bipolar subjects is with regard to depressive rather than manic symptoms [100],[101].

Osher and colleagues [102] treated 12 bipolar I depressed subjects with open adjunctive EPA, 1.5 to 2 g/d, for up to 6 months. Ten patients completed at least 1 month of follow-up, and eight achieved a 50% or greater reduction in HAM-D scores. No cycling occurred with any patients.

Further investigation is needed to determine whether bipolar disorder actually requires higher doses of omega-3 fatty acids than unipolar illness and to unravel the respective contributions of EPA and DHA.

The relationship between omega-3 fatty acid treatment and a range of other psychiatric syndromes also has been studied to a lesser extent; the resulting data are equivocal. Conditions investigated include borderline personality disorder, schizophrenia, attention-deficit disorder, and obsessive-compulsive disorder [103], [104], [105], [106], [107], [108], [109], [110]. These investigations tend to consist of smaller patient samples, and their conflicting results reflect this limitation.

Safety and Tolerability

The omega-3s have been shown to be very safe. Most complaints of side effects such as gastrointestinal upset and fishy aftertaste tend to occur with higher doses (>5 g/d) and with less pure preparations. At the more typical doses of 1 g/d with highly purified omega-3 preparations, these adverse effects are less common. There is a documented risk of bleeding, which seems to be minimal, particularly with doses less than 3 g/d. Individuals taking anticoagulants such as warfarin need to be careful, and should not use omega-3s without physician supervision [83]. Given a few documented cases of cycling in bipolar patients [83], omega-3s should be used with care in this population and preferably with a concomitant mood stabilizer.

Recommendations and Special Considerations for Women who are Pregnant or Breastfeeding

The data supporting use of omega-3 fatty acids for depression are encouraging, particularly with regard to EPA. Low doses of omega-3 fatty acids may be effective and well-tolerated monotherapy or adjunctive therapy for depressed adults. A recent review by Freeman and colleagues [83] recommends that depressed individuals may safely use approximately 1 g/d of an EPA-DHA mixture but should not substitute omega-3s for conventional antidepressants at this time. Likewise, individuals who take more than 3 g/d of omega-3 should do so under a physician's supervision [83].

Most studies thus far have used omega-3s as adjunctive agents; given their apparent safety and tolerability, their effectiveness as monotherapy should be investigated further. Likewise, the issue of whether EPA or DHA is more effective in the treatment of depression remains to be clarified. Finally, the mechanism of action of the omega-3s, particularly their interplay with the immune system, merits further investigation. Studies addressing these questions are currently underway at the MGH and Cedars-Sinai Medical Center. It is hoped that these and other future investigations will clarify some of the lingering unanswered questions about this exciting and potentially valuable treatment.

The omega-3 fatty acids may be particularly well suited for treatment of specific patient populations (eg, pregnant or lactating women) for whom antidepressants must be used with caution [111], for elderly people who may not tolerate side effects of conventional antidepressants agents, and for those who have medical comorbidity, particularly cardiovascular disease and possibly autoimmune conditions, for which there may be dual benefits. That said, it remains difficult to recommend omega-3s as a first-line antidepressant during pregnancy, in view of the well documented safety and efficacy of the tricyclic antidepressants and the selective serotonin reuptake inhibitors (SSRIs). Various lines of investigation have demonstrated benefit from omega-3s to expectant mothers, in who fish intake is often restricted during pregnancy, and to unborn children and infants, particularly with regard to neural development [112],[113] and allergy prevention [114]. However, it is not

known what the safe upper limit of omega-3 supplements may be in pregnancy [113]. Pregnant women who are depressed and are considering omega-3 therapy should first discuss the matter with their physician and consider a consultation with a psychiatrist who is well versed in the use of natural products.

Summary

Natural medications such as St. John's Wort, SAME, and omega-3 fatty acids eventually may prove to be valuable additions to the pharmacologic armamentarium, both as monotherapy and as adjunctive therapy for mood disorders. Current research data are compelling, from a standpoint of both efficacy and safety, but before clinicians can recommend these as first-line treatments, more well-designed controlled studies in large patient populations are needed. During the past decade, the National Institutes of Health, the National Institute for Mental Health, and the National Center for Complementary and Alternative Medicine have widened their support for research on the efficacy and safety of alternative treatments, and increasing numbers of academic institutions are undertaking large-scale, multicenter studies on the natural medications reviewed here, as well as others. These studies should help answer some of the yet-unsettled questions about natural medications.

Physicians who are considering recommending natural antidepressants to their patients should emphasize that these treatments are relatively unproven and that it remains to be seen whether they would be appropriate or preferable to the conventional psychotropic agents [115], [116]. In the absence of more conclusive data, the best candidates for alternative treatments may be patients for whom a delay in adequate treatment would not be devastating (eg, the mildly symptomatic patient who has a strong interest in natural remedies). Other good candidates may include patients who have been unresponsive to conventional antidepressants or particularly intolerant of side effects; these patients, however, often are the most difficult to treat, and alternative agents seem best suited for the mildly ill [116]. Care should be taken with patients who are taking multiple medications, in view of adverse drug–drug interactions that have emerged with increased use of alternative treatments. Pregnant women are probably safer using registered antidepressants, though current knowledge suggests that the omega-3 fatty acids and SAME should eventually be proven safe in pregnancy. St. John's wort, in view of its documented interactions and presence of myriad plant-derived chemicals of unknown significance, will require more rigorous safety testing before it can be recommended in pregnancy. Finally, as with all psychotropic agents, natural medications should be used preferably under the supervision of a physician.

Box 1: S-adenosyl methionine

This derivative of the amino acid methionine functions by donating a methyl (-CH₃) group in a variety of metabolic reactions, including the synthesis of neurotransmitters.

Box 2: Docosahexaenoic acid and eicosapentaenoic acid*Docosahexaenoic acid*

Docosahexaenoic acid (22:6, n-3) has a 22-carbon chain and six double bonds. The leftmost carbon is termed the “omega” carbon, and the first double bond occurs on the third carbon from the left, hence the term “omega-3.”

Eicosapentaenoic acid

Eicosapentaenoic acid (20:5, n-3) has a 20-carbon chain and five double bonds. The first double bond occurs on the third carbon from the left.

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References

- Schulz, V.; Hansel, R.; Tyler, VE. Rational phytotherapy: a physician's guide to herbal medicine. Vol. 4th edition. Springer; Berlin: 2001. p. 78-86.
- National Institutes of Health Office of Alternative Medicine 1997. Clinical practice guidelines in complementary and alternative medicine. An analysis of opportunities and obstacles. Practice and Policy Guidelines Panel. Arch Fam Med 1997;6:149–154. [PubMed: 9075450]
- Eisenberg DM, Kessler RC, Foster C, et al. Unconventional medicine in the United States: prevalence, costs, and patterns of use. N Engl J Med 1993;328:246–252. [PubMed: 8418405]
- Krippner S. A cross cultural comparison of four healing models. Alternative therapies. Health and Medicine 1995;1:21–29.
- Mischoulon D. Nutraceuticals in psychiatry, part 1: social, technical, economic, and political perspectives. Contemporary Psychiatry 2004;2(11):1–6.
- Mischoulon D. Nutraceuticals in psychiatry, part 2: review of six popular psychotropics. Contemporary Psychiatry 2004;3(1):1–8.
- National Institutes of Health Office of Alternative Medicine. Alternative medicine: expanding medical horizons. National Institutes of Health Office of Alternative Medicine; Rockville (MD): 1992.
- Muller-Kuhrt L, Boesel R. Analysis of hypericins in hypericum extract. Nervenheilkunde 1993;12:359–361.
- Staffeldt B, Kerb R, Brockmoller J, et al. Pharmacokinetics of hypericin and pseudohypericin after oral intake of the Hypericum perforatum extract LI 160 in healthy volunteers. Nervenheilkunde 1993;12:331–338.
- Wagner H, Bladt S. Pharmaceutical quality of hypericum extracts. Nervenheilkunde 1993;12:362–366.
- Müller W, Rossol R. Effects of hypericum extract on the expression of serotonin receptors. Nervenheilkunde 1993;12:357–358.

12. Thiele B, Ploch M, Brink I. Modulation of cytokine expression by hypericum extract. *Nevenheilkunde* 1993;12:353–356.
13. Teufel-Mayer R, Gleitz J. Effects of long-term administration of hypericum extracts on the affinity and density of the central serotonergic 5-HT_{1A} and 5-HT_{2A} receptors. *Pharmacopsychiatry* 1997;30 (Suppl 2):113–116. [PubMed: 9342771]
14. Nierenberg, AA.; Lund, HG.; Mischoulon, D. St. John's wort: a critical evaluation of the evidence for antidepressant effects.. In: Mischoulon, D.; Rosenbaum, J., editors. *Natural medications for psychiatric disorders: considering the alternatives*. Vol. 2nd edition. Lippincott Williams & Wilkins; Philadelphia: 2008. p. 27-38.
15. Laakmann G, Schule C, Baghai T, et al. St. John's Wort in mild to moderate depression: the relevance of hyperforin for the clinical efficacy. *Pharmacopsychiatry* 1998;31(Suppl 1):54–59. [PubMed: 9684948]
16. Orth HC, Rentel C, Schmidt PC. Isolation, purity analysis and stability of hyperforin as a standard material from *Hypericum perforatum* L. *J Pharm Pharmacol* 1999;51(2):193–200. [PubMed: 10217319]
17. Bladt S, Wagner H. MAO inhibition by fractions and constituents of hypericum extract. *Nervenheilkunde* 1993;12:349–352.
18. Linde K, Mulrow CD, Berner M, et al. St John's wort for depression. *Cochrane Database Syst Rev* 2005;(2):CD000448. [PubMed: 15846605]
19. Vorbach EU, Hubner WD, Arnoldt KH. Effectiveness and tolerance of the hypericum extract LI 160 in comparison with imipramine. Randomized double blind study with 135 outpatients. *Nevenheilkunde* 1993;12:290–296. Also in *J Geriatr Psychiatry Neurol* 1994 Oct;7 Suppl 1:S19–23
20. Harrer G, Hubner WD, Podzuweit H. Effectiveness and tolerance of the hypericum preparation LI 160 compared to maprotiline. Multicentre double-blind study with 102 outpatients. *Nervenheilkunde* 1993;12:297–301.
21. Martinez B, Kasper S, Ruhmann B, et al. Hypericum in the treatment of seasonal affective disorders. *Nervenheilkunde* 1993;12:302–307.
22. Wheatley D. LI 160, an extract of St. John's wort, versus amitriptyline in mildly to moderately depressed outpatients—a controlled 6-week clinical trial. *Pharmacopsychiatry* 1997;30(Suppl 2):77–80. [PubMed: 9342764]
23. Nierenberg AA. St. John's Wort: a putative over-the-counter herbal antidepressant. *Journal of Depressive Disorders, Index & Reviews* 1998;III:16–17.
24. Linde K, Ramirez G, Mulrow CD, et al. St. John's wort for depression—an overview and meta-analysis of randomized clinical trials. *Br Med J* 1996;313:253–258. [PubMed: 8704532]
25. Volz HP. Controlled clinical trials of hypericum extracts in depressed patients—an overview. *Pharmacopsychiatry* 1997;30(Suppl 2):72–76. [PubMed: 9342763]
26. Lecrubier Y, Clerc G, Didi R, et al. Efficacy of St. John's wort extract WS 5570 in major depression: a double-blind, placebo-controlled trial. *Am J Psychiatry* 2002;159(8):1361–1366. [PubMed: 12153829]
27. Shelton RC, Keller MB, Gelenberg A, et al. Effectiveness of St John's wort in major depression: a randomized controlled trial. *JAMA* 2001;285(15):1978–1986. [PubMed: 11308434]
28. Brenner R, Azbel V, Madhusoodanan S, et al. Comparison of an extract of hypericum (LI 160) and sertraline in the treatment of depression: a double-blind, randomized pilot study. *Clin Ther* 2000;22 (4):411–419. [PubMed: 10823363]
29. Gastpar M, Singer A, Zeller K. Efficacy and tolerability of hypericum extract STW3 in long-term treatment with a once-daily dosage in comparison with sertraline. *Pharmacopsychiatry* 2005;38(2): 78–86. [PubMed: 15744631]
30. van Gurp G, Meterissian GB, Haiek LN, et al. St John's wort or sertraline? Randomized controlled trial in primary care. *Can Fam Physician* 2002;48:905–912. [PubMed: 12053635]
31. Schrader E. Equivalence of St John's wort extract (Ze 117) and fluoxetine: a randomized, controlled study in mild-moderate depression. *Int Clin Psychopharmacol* 2000;15(2):61–68. [PubMed: 10759336]
32. Behnke K, Jensen GS, Graubaus HJ, et al. Hypericum perforatum versus fluoxetine in the treatment of mild to moderate depression. *Adv Ther* 2002;19(1):43–52. [PubMed: 12008860]

33. Hypericum Depression Trial Study Group. Effect of Hypericum perforatum (St John's wort) in major depressive disorder: a randomized controlled trial. *JAMA* 2002;287:1807–1814. [PubMed: 11939866]
34. Fava M, Alpert J, Nierenberg AA, et al. A double-blind, randomized trial of St. John's Wort, fluoxetine, and placebo in major depressive disorder. *J Clin Psychopharmacol* 2005;25(5):441–447. [PubMed: 16160619]
35. Moreno RA, Teng CT, Almeida KM, et al. Hypericum perforatum versus fluoxetine in the treatment of mild to moderate depression: a randomized double-blind trial in a Brazilian sample. *Rev Bras Psiquiatr* 2006;28(1):29–32. [PubMed: 16612487][Epub 2006 Mar 24]
36. Baede-van Dijk PA, van Galen E, Lekkerkerker JF. [Drug interactions of Hypericum perforatum (St. John's wort) are potentially hazardous]. *Ned Tijdschr Geneesk* 2000;144(17):811–812. [PubMed: 10800553](Article in Dutch)
37. Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. *Arch Intern Med* 1998;158:2200–2211. [PubMed: 9818800]
38. Moore LB, Goodwin B, Jones SA, et al. St. John's wort induces hepatic drug metabolism through activation of the pregnane X receptor. *Proc Natl Acad Sci U S A* 2000;97(13):7500–7502. [PubMed: 10852961]
39. Miller JL. Interaction between indinavir and St. John's wort reported. *Am J Health Syst Pharm* 2000;57(7):625–626.
40. Piscitelli SC, Burstein AH, Chait D, et al. Indinavir concentrations and St John's wort. *Lancet* 2000;355(9203):547–548. [PubMed: 10683007]
41. Hu Z, Yang X, Ho PC, et al. Herb-drug interactions: a literature review. *Drugs* 2005;65(9):1239–1282. [PubMed: 15916450]
42. Schulz V. Safety of St. John's Wort extract compared to synthetic antidepressants. *Phytomedicine* 2006;13(3):199–204. [PubMed: 16428030][Epub 2005 Nov 2]
43. Woelk H, Burkhard G, Grunwald J. Evaluation of the benefits and risks of the hypericum extract LI 160 based on a drug monitoring study with 3250 patients. *Nervenheilkunde* 1993;12:308–313.
44. Beattie PE, Dawe RS, Traynor NJ, et al. Can St John's wort (hypericin) ingestion enhance the erythral response during high-dose ultraviolet A1 therapy?. *Br J Dermatol* 2005;153(6):1187–1191. [PubMed: 16307656]
45. Brockmoller J, Reum T, Bauer S, et al. Hypericin and pseudohypericin: pharmacokinetics and effects on photosensitivity in humans. *Pharmacopsychiatry* 1997;30(Suppl 2):94–101. [PubMed: 9342768]
46. Siegers CP, Biel S, Wilhelm KP. Phototoxicity caused by hypericum. *Nervenheilkunde* 1993;12:320–322.
47. Stevinson C, Ernst E. Can St. John's wort trigger psychoses?. *Int J Clin Pharmacol Ther* 2004;42(9):473–480. [PubMed: 15487805]
48. Dugoua JJ, Mills E, Perri D, Koren G. Safety and efficacy of St. John's wort (hypericum) during pregnancy and lactation. *Can J Clin Pharmacol* 2006;13(3):e268–76. [PubMed: 17085775][FallEpub 2006 Nov 3]
49. Moretti ME, Maxson A, Hanna F, Koren G. Evaluating the safety of St. John's Wort in human pregnancy. *Reprod Toxicol* Jul;2009 28(1):96–9. [PubMed: 19491000][Epub 2009 Feb 24]
50. Klier CM, Schäfer MR, Schmid-Siegel B, Lenz G, Mannel M. St. John's wort (Hypericum perforatum)--is it safe during breastfeeding? *Pharmacopsychiatry* Jan;2002 35(1):29–30. [PubMed: 11819157]
51. Klier CM, Schmid-Siegel B, Schäfer MR, Lenz G, Saria A, Lee A, Zernig G. St. John's wort (Hypericum perforatum) and breastfeeding: plasma and breast milk concentrations of hyperforin for 5 mothers and 2 infants. *J Clin Psychiatry* Feb;2006 67(2):305–9. [PubMed: 16566628]
52. Lee A, Minhas R, Matsuda N, Lam M, Ito S. The safety of St. John's wort (Hypericum perforatum) during breastfeeding. *J Clin Psychiatry* Aug;2003 64(8):966–8. [PubMed: 12927015]
53. Freeman MP. Complementary and alternative medicine for perinatal depression. *J Affect Disord* Jan; 2009 112(13):1–10. [PubMed: 18692251][Epub 2008 Aug 8]
54. Spillmann M, Fava M. S-adenosyl-methionine (ademethionine) in psychiatric disorders. *CNS Drugs* 1996;6:416–425.

55. Alpert JE, Mischoulon D, Nierenberg AA, et al. Nutrition and depression: focus on folate. *Nutrition* 2000;16:544–546. [PubMed: 10906550]
56. Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial. *J Affect Disord* 2000;60:121–130. [PubMed: 10967371]
57. Alpert JE, Mischoulon D, Rubenstein GEF, et al. Folinic acid (Leucovorin) as an adjunctive treatment for SSRI-refractory depression. *Ann Clin Psychiatry* 2002;14:33–38. [PubMed: 12046638]
58. Fava M, Borus JS, Alpert JE, et al. Folate, B12, and homocysteine in major depressive disorder. *Am J Psychiatr* 1997;154:426–428. [PubMed: 9054796]
59. Bottiglieri T, Godfrey P, Flynn T, et al. Cerebrospinal fluid s-adenosylmethionine in depression and dementia: effects of treatment with parenteral and oral s-adenosylmethionine. *J Neurol Neurosurg Psychiatr* 1990;53:1096–1098. [PubMed: 2292704]
60. Bell KM, Potkin SG, Carreon D, et al. S-adenosylmethionine blood levels in major depression: changes with drug treatment. *Acta Neurol Scand Suppl* 1994;154:15–18. [PubMed: 7941961]
61. Bottiglieri T, Chary TK, Laundry M, et al. Transmethylation in depression. *Ala J Med Sci* 1988;25:296–301. [PubMed: 3052137]
62. Matthyse S, Baldessarini RJ. S-adenosylmethionine and catechol-O-methyl-transferase in schizophrenia. *Am J Psychiatry* 1972;128:1310–1312. [PubMed: 5013751]
63. Tolbert LC. MAT kinetics in affective disorders and schizophrenia. An account. *Ala J Med Sci* 1988;25:291–296. [PubMed: 3177804]
64. Bressa GM. S-Adenosyl-L-Methionine (SAME) as antidepressant: meta-analysis of clinical studies. *Acta Neurol Scand* 1994;154(Suppl):7–14.
65. Papakostas GI, Alpert JE, Fava M. S-Adenosyl methionine in depression: a comprehensive review of the literature. *Curr Psychiatry Rep* 2003;5:460–466. [PubMed: 14609501]
66. Mischoulon D, Fava M. Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence. *Am J Clin Nutr* 2002;76(5 Suppl):1158S–1161S. [PubMed: 12420702]
67. Fava M, Giannelli A, Rapisarda V, et al. Rapidity of onset of the antidepressant effect of parenteral S-adenosyl-L-methionine. *Psychiatry Res* 1995;56:295–297. [PubMed: 7568552]
68. Alvarez E, Udina C, Guillamat R. Shortening of latency period in depressed patients treated with SAME and other antidepressant drugs. *Cell Biol Rev* 1987;S1:103–110.
69. Berlanga C, Ortega-Soto HA, Ontiveros M, et al. Efficacy of S-adenosyl-L-methionine in speeding the onset of action of imipramine. *Psychiatry Res* 1992;44:257–262. [PubMed: 1289923]
70. Alpert JE, Papakostas G, Mischoulon D, et al. 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* 2004;24(6):661–664. [PubMed: 15538131]
71. Carney MWP, Chary TNK, Bottiglieri T. Switch mechanism in affective illness and oral S-adenosylmethionine (SAM). *Br J Psychiatry* 1987;150:724–725. [PubMed: 3651725]
72. Carney MW, Martin R, Bottiglieri T, et al. Switch mechanism in affective illness and S-adenosylmethionine. *Lancet* 1983;1:820–821. [PubMed: 6132153]
73. Guerra-Shinohara EM, Morita OE, Peres S, Pagliusi RA, Sampaio Neto LF, D'Almeida V, Irazusta SP, Allen RH, Stabler SP. Low ratio of S-adenosylmethionine to S-adenosylhomocysteine is associated with vitamin deficiency in Brazilian pregnant women and newborns. *Am J Clin Nutr* Nov; 2004 80(5):1312–21. [PubMed: 15531681]
74. Frezza M, Surrenti C, Manzillo G, Fiaccadori F, Bortolini M, Di Padova C. Oral S-adenosylmethionine in the symptomatic treatment of intrahepatic cholestasis. A double-blind, placebo-controlled study. *Gastroenterology* Jul;1990 99(1):211–5. [PubMed: 2188871]
75. Adams PB, Lawson S, Sanigorski A, et al. Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids* 1996;31:157–161.
76. Hibbeln JR, Salem N. Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. *Am J Clin Nutr* 1995;62:1–9. [PubMed: 7598049]
77. Cross-National Collaborative Group. The changing rate of major depression: cross national comparisons. *JAMA* 1992;268:3098–3105. [PubMed: 1433741]

78. Hibbeln JR. Fish consumption and major depression. *Lancet* 1998;351:1213. [PubMed: 9643729] [letter]
79. Hibbeln, JR. Long-chain polyunsaturated fatty acids in depression and related conditions.. In: Peet, M.; Glen, I.; Horrobin, DF., editors. *Phospholipid spectrum disorder in psychiatry*. Marius Press; Carnforth (UK): 1999. p. 195-210.
80. Stoll, AL. Omega-3 fatty acids in mood disorders: a review of neurobiological and clinical actions.. In: Mischoulon, D.; Rosenbaum, J., editors. *Natural Medications for Psychiatric Disorders: Considering the Alternatives*. Lippincott Williams & Wilkins; Philadelphia: 2008. p. 39-67.
81. Hamazaki K, Itomura M, Huan M, et al. Effect of omega-3 fatty acid-containing phospholipids on blood catecholamine concentrations in healthy volunteers: a randomized, placebo-controlled, double-blind trial. *Nutrition* 2005;21(6):705–710. [PubMed: 15925295]
82. Murck H, Song C, Horrobin DF, et al. Ethyl-eicosapentaenoate and dexamethasone resistance in therapy-refractory depression. *Int J Neuropsychopharmacol* 2004;7(3):341–349. [PubMed: 15003146]
83. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatr* 2006;67:1954–1967.
84. Appleton KM, Hayward RC, Gunnell D, et al. Effects of n-3 long-chain polyunsaturated fatty acids on depressed mood: systematic review of published trials. *Am J Clin Nutr* 2006;84(6):1308–1316. [PubMed: 17158410]
85. Lin PY, Su KP. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *J Clin Psychiatry* 2007;68(7):1056–1061. [PubMed: 17685742]
86. Rogers PJ, Appleton KM, Kessler D, et al. No effect of n-3 long-chain polyunsaturated fatty acid (EPA and DHA) supplementation on depressed mood and cognitive function: a randomised controlled trial. *Br J Nutr* 2008;99(2):421–431. [PubMed: 17956647]
87. Peet M, Horrobin DF. 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* 2002;59(10):913–919. [PubMed: 12365878]
88. Su KP, Huang SY, Chiu CC, et al. Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. *Eur Neuropsychopharmacol* 2003;13(4):267–271. [PubMed: 12888186]
89. Nemets B, Stahl ZM, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry* 2002;159:477–479. [PubMed: 11870016]
90. Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. *Br J Psychiatry* 2006;188:46–50. [PubMed: 16388069]
91. Mischoulon D, Papakostas GI, Dording CM, Farabaugh AH, Sonawalla SB, Agoston M, Smith J, Beaumont E, Dahan L, Alpert JE, Nierenberg AA, Fava M. A double-blind randomized controlled trial of ethyl-eicosapentaenoate (EPA-E) for major depressive disorder. *J Clin Psychiatry*. (in press)
92. Silvers KM, Woolley CC, Hamilton FC, et al. Randomized double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukot Essent Fatty Acids* 2005;72:211–218. [PubMed: 15664306]
93. Marangell LB, Martinez JM, Zboyan HA, et al. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry* 2003;160(5):996–998. [PubMed: 12727707]
94. Mischoulon D, Best-Popescu C, Laposata M, Merens W, Murakami JL, Wu S, Papakostas GI, Dording CM, Sonawalla SB, Nierenberg AA, Alpert JE, Fava M. A double-blind dose-finding pilot study of docosahexaenoic acid (DHA) for major depressive disorder. *Eur Neuropsychopharm* 2008;18:639–645.
95. Freeman MP, Hibbeln JR, Wisner KL, et al. Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression. *Acta Psychiatr Scand* 2006;113(1):31–35. [PubMed: 16390366]
96. Marangell LB, Martinez JM, Zboyan HA, et al. Omega-3 fatty acids for the prevention of postpartum depression: negative data from a preliminary, open-label pilot study. *Depress Anxiety* 2004;19(1):20–23. [PubMed: 14978781]

97. Strøm M, Mortensen EL, Halldorsson TI, Thorsdottir I, Olsen SF. Fish and long-chain n-3 polyunsaturated fatty acid intakes during pregnancy and risk of postpartum depression: a prospective study based on a large national birth cohort. *Am J Clin Nutr* Jul;2009 90(1):149–55. [PubMed: 19474139][Epub 2009 May 27]
98. Stoll AL, Severus EW, Freeman MP, et al. Omega3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1999;56:407–412. [PubMed: 10232294]
99. Keck PE, Mintz J, McElroy SL, et al. Double-blind, randomized, placebo-controlled trials of ethyl-eicosapentaenoate in the treatment of bipolar depression and rapid cycling bipolar disorder. *Biol Psychiatry* 2006;60:1020–1022. [PubMed: 16814257]
100. Parker G, Gibson NA, Brotchie H, et al. Omega-3 fatty acids and mood disorders. *Am J Psychiatry* 2006;163(6):969–978. [PubMed: 16741195]
101. Montgomery P, Richardson AJ. Omega-3 fatty acids for bipolar disorder. *Cochrane Database Syst Rev* 2008;(2):CD005169. [PubMed: 18425912]
102. Osher Y, Bersudsky Y, Belmaker RH. Omega-3 eicosapentaenoic acid in bipolar depression: report of a small open-label study. *J Clin Psychiatry* 2005;66(6):726–729. [PubMed: 15960565]
103. Zanarini MC, Frankenburg FR. Omega-3 fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *Am J Psychiatry* 2003;160:167–169. [PubMed: 12505817]
104. Mellor JE, Laugharne JDE, Peet M. Omega-3 fatty acid supplementation in schizophrenic patients. *Hum Psychopharmacol* 1996;11:39–46.
105. Vaddadi KS, Courtney T, Gilleard CJ, et al. A double-blind trial of essential fatty acid supplementation in patients with tardive dyskinesia. *Psychiatry Res* 1989;27:313–323. [PubMed: 2565585]
106. Emsley R, Myburgh C, Oosthuizen P, et al. Randomized, placebo-controlled study of ethyl-eicosapentaenoic acid as supplemental treatment in schizophrenia. *Am J Psychiatry* 2002;159:1596–1588. [PubMed: 12202284]
107. Fenton WS, Dickerson F, Boronow J, et al. A placebo-controlled trial of omega-3 fatty acid (ethyl eicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. *Am J Psychiatry* 2001;158:2071–2074. [PubMed: 11729030]
108. Maidment ID. Are fish oils an effective therapy in mental illness—an analysis of the data. *Acta Psychiatr Scand* 2000;102:3–11. [PubMed: 10892603]
109. Fux M, Benjamin J, Nemets B. A placebo-controlled cross-over trial of adjunctive EPA in OCD. *J Psychiatr Res* 2004;38(3):323–325. [PubMed: 15003438]
110. Peet M, Brind J, Ramchand CN, et al. Two double-blind placebo-controlled pilot studies of eicosapentaenoic acid in the treatment of schizophrenia. *Schizophr Res* 2001;49(3):243–251. [PubMed: 11356585]
111. Chiu C-C, Huang S-Y, Shen WW, et al. Omega-3 fatty acids for depression in pregnancy. *Am J Psychiatry* 2003;160:385. [PubMed: 12562593][letter]
112. Greenberg JA, Bell SJ, Ausdal WV. Omega-3 Fatty Acid supplementation during pregnancy. *Rev Obstet Gynecol* 2008;1(4):162–9. [PubMed: 19173020]Fall
113. Innis SM. Omega-3 Fatty acids and neural development to 2 years of age: do we know enough for dietary recommendations? *J Pediatr Gastroenterol Nutr* Mar;2009 48(Suppl 1):S16–24. [PubMed: 19214053]
114. Furuholm C, Warstedt K, Larsson J, Fredriksson M, Böttcher MF, Fälth-Magnusson K, Duchén K. Fish oil supplementation in pregnancy and lactation may decrease the risk of infant allergy. *Acta Paediatr*. Jun 1;2009 [Epub ahead of print]
115. Eisenberg DM. Advising patients who seek alternative medical therapies. *Ann Intern Med* 1997;127(1):61–69. [PubMed: 9214254]
116. Mischoulon D, Rosenbaum JF. The use of natural medications in psychiatry: a commentary. *Harv Rev Psychiatry* 1999;6:279–283. [PubMed: 10372293]