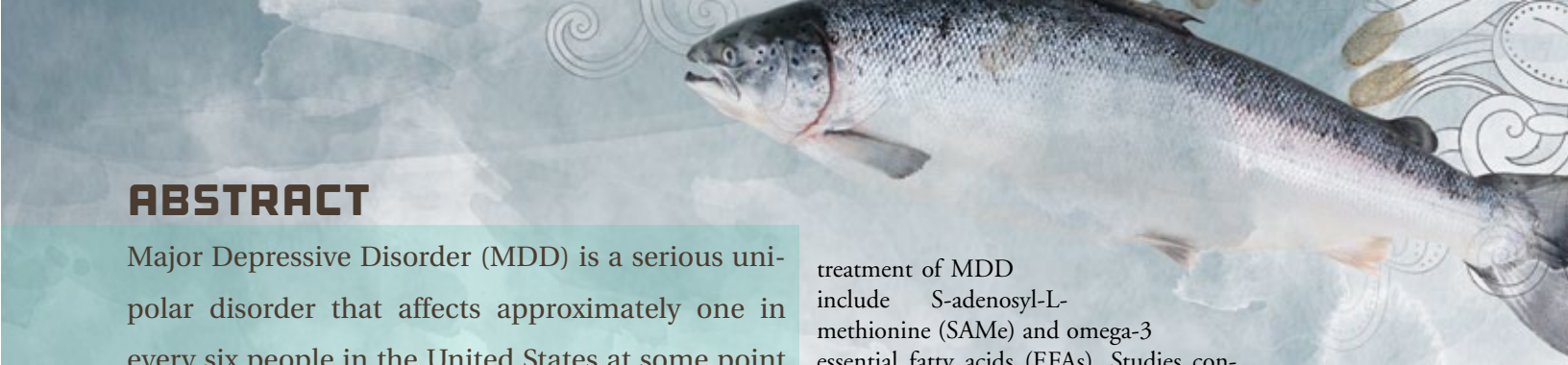
2 KEY NUTRIENTS for the treatment of MAJOR DEPRESSIVE DISORDER

by Ryan Harrison



ABSTRACT

Major Depressive Disorder (MDD) is a serious unipolar disorder that affects approximately one in every six people in the United States at some point in their lives. With the recent swell of public interest in Complementary and Alternative Medicine (CAM), people with mood disorders such as MDD are turning increasingly to non-medical treatment alternatives such as nutritional supplementation. Two well-studied nutrients that have been used in the treatment of MDD are S-adenosyl-L-methionine (SAMe) and omega-3 essential fatty acids (EFAs). Both have shown efficacy as stand-alone and adjuvant treatments, although additional research is necessary to determine appropriate clinical usage.

Nutritional Approaches to the Treatment of Major Depressive Disorder

Major Depressive Disorder (MDD) is a unipolar mood disorder experienced by as many as one in every six people in the U.S. (Sarris, Schoendorfer, & Kavanagh, 2009). Its prevalence makes it one of the most common reasons people seek medical attention. Butcher, Mineka, and Hooley (2010) reported that three of the eleven most prescribed drugs in the United States are medications used to treat depression. Many people who take medication for MDD may develop any number of adverse reactions including dry mouth, constipation, sexual dysfunction, insomnia, weight gain, and even death (Butcher, Mineka, & Hooley, 2010). Compounding the issue, Mischoulon and Fava (2002) reported that, "between 19% and 34% of depressed patients…do not respond to acute antidepressant treatment, 29-46% may fail to achieve and sustain a full remission, and between 15% and 50% will have a recurrence of depression despite continuous antidepressant treatment" (p. 1158S).

In an effort to find effective treatment for their medical concerns without such potential side effects, many people turn to Complementary and Alternative Medicine (CAM). Between 36% and 42% of U.S. adults utilize some form of CAM within a twelve-month period, most commonly for conditions treated by psychologists, including depression (Tippens, Marsman, & Zwickey, 2009; White, 2009). Indeed, White (2009) found that "persons suffering from depression and anxiety…use CAM services significantly more than do their nonanxious and nondepressed counterparts" (p. 633). With the rise of CAM use in the treatment of psychological disorders, research into nutritional approaches has grown. Two of the most widely researched nutritional supplements useful in the treatment of MDD include S-adenosyl-L-methionine (SAMe) and omega-3 essential fatty acids (EFAs). Studies confirm these supplements' use as adjuvant and, in some instances, stand-alone therapies, although more research is necessary to determine precise clinical applications of these two supplements.

Major Depressive Disorder

Major Depressive Disorder (MDD) is a common unipolar disorder marked by low mood or loss of pleasure occurring in tandem with changes in appetite, sleep patterns, energy, or concentration, and typically accompanied by feelings of worthlessness, hopelessness, guilt, or suicidal thoughts (Butcher et al., 2010; Sarris et al., 2009). It is also recurrent, with untreated episodes lasting typically between six and nine months; in severe cases, symptoms may not remit for over two years (Butcher et al., 2010).

The etiology of MDD is uncertain, although there may be several factors involved in any given person's experience. Biological factors include genetics; Butcher et al. (2010) reported that genetics may account for anywhere between 31% to 80%, depending on several features including severity, age of onset, and recurrence. The neurochemicals noepinephrine, serotonin, and dopamine have also been implicated, although research is still determining exact relationships. Hormonal abnormalities have been seen in depressed people; levels of cortisol are typically elevated in 20% to 80% of outpatient and hospitalized depressed people (Butcher et al., 2010). Damage to certain areas of the brain may lead to depression, as well. The orbital prefrontal cortex, hippocampus, left anterior prefrontal cortex, anterior cingulated cortex, and the amygdala have each been connected to incidences of clinical depression (Butcher et al., 2010). Finally, if a person has a diathesis toward depression or a neurotic personality, exhibiting sensitivity to negative stimuli, life experiences such as early adversity, trauma, or loss of a parent may precipitate an episode of depression (Butcher et al., 2010).

Standard treatment of MDD includes the pharmacotherapeutic use of antidepressants, mood-stabilizers, and antipsychotic drugs. Typically, monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRIs) have been prescribed. Although they have shown to be no more effective than their predecessors, SSRIs have become the primary prescription of choice in recent years. This is due to SSRIs' fewer side effects, better toleration by patients, and less toxicity at large doses (Butcher et al., 2010).

Psychotherapy has also been successfully employed in the treatment of depression. Cognitive-behavior therapy, behavioral activation treatment, interpersonal therapy, and family therapy have each displayed positive results in mitigating the symptoms of depression, equal to medication treatment alone. Further, "considerable evidence also suggests that…psychotherapy for depression, alone or in combination with drugs, significantly decrease(s) the likelihood of relapse within a 2-year follow-up period" (Butcher et al., 2010, p. 259).

SAMe

At times, however, depressed people are at pains to rely on prescription medication, or do not have access to, or sufficient financial means, to engage in psychotherapy. In these cases, they may turn instead to CAM (White, 2009). One of the most robust areas of CAM is nutritional supplementation, and among the supplements chiefly turned to for mood support is SAMe. Known colloquially by its far less imposing name, SAMe, S-adenosyl-L-methionine is "a major methyl donor in the brain that is involved in the pathways for synthesis of hormones, neurotransmitters, nucleic acids, proteins, and phospholipids" (Mischoulon & Fava, 2002, p. 1158S). SAMe is required, for example, in the synthesis of the neurotransmitters norepinephrine, dopamine, and serotonin, each of which is connected to mood and psychological well-being. No direct link between SAMe and depression has been discovered, though several lines of evidence suggest a strong connection. For example, Mischoulon and Fava (2002) reported that low levels of SAMe have been noted in the cerebral spinal fluid of depressed persons; there is a direct, positive correlation between raised plasma levels of SAMe and improvement of depressive symptoms; and where manic patients tend to be high in an enzyme required in the formation of SAMe, depressed patients show low levels.

Many studies have investigated the use of SAMe in the treatment of depression. Sarris, Schoendorfer, and Kavanagh (2009) noted that SAMe has consistently exhibited antidepressant properties, "with effects comparable to those of synthetic antidepressants" (p. 128). In human trials assessing the efficacy of SAMe in treating MDD, subjects given SAMe consistently benefitted and tended to do so faster than is typical in antidepressant treatment (Mischoulon & Fava, 2002; Sarris et al., 2009). As an adjuvant therapy, SAMe has been shown to increase the efficacy and speed of response to antidepressants such as SSRIs, venlafaxine, and imipramine (Sarris et al., 2009).

However, broad therapeutic usage of SAMe remains somewhat problematic. Because most studies have focused on parenteral (intravenous or intramuscular) injections of the supplement in wide-ranging dosages, there is no clear indicator of how to best use SAMe in oral (tablet) form. Mischoulon and Fava (2002) noted that one study suggested the effective dosage range to be between 800-3600 mg/day. However, this was in the treatment of Parkinson's Disease and not MDD specifically. Even so, SAMe seems to be free of severe, adverse effects with "no apparent associated hepatotoxicity or anticholinergic effects" (Mischoulon & Fava, 2002, p. 1159S). Minor side effects have been noted including mild insomnia, lack of appetite, sweating, nausea, and nervousness. One notable restriction on the use of SAMe is that patients with bipolar disorders should not use it unless they are also taking a mood stabilizing drug, as SAMe has evinced some increase in anxiety, mania, and hypomania in such patients (Mischoulon & Fava, 2002).

Omega-3 Fatty Acids

A second nutritional approach to the treatment of depression concerns the use of omega-3 fatty acids, a member of the polyunsaturated fatty acid (PUFA) group, sometimes also referred to as essential fatty acids (EFAs). Closely related to omega-3s are the omega-6 PUFAs. The typical U.S. diet tends to be high in pro-inflammatory omega-6s and low in anti-inflammatory omega-3s (Zurfluh & Shapses, 2008), a ratio that has strong associations with "increased rates of depression, seasonal affective disorder, anxiety, and suicide" (Williams et al., 2006, p. 121). Omega-3s are characteristically researched in terms of their distinct PUFA components, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). DHA is known to constitute a large portion of the brain's lipid profile, is important in the central nervous system, is integral to neuronal structure and health, and is directly connected to neurobehavioral development (Logan, 2006; Milte, Sinn, & Howe, 2009; Williams et al., 2006). EPA is involved in the production of hormone-like compounds that regulate cell division and growth and govern the secretion of hormones, and is known to have anti-inflammatory characteristics via its role in the suppression of pro-inflammatory cytokines (Office of Dietary Supplements, 2005).

Many studies have investigated the use of omega-3s in the treatment of depression and have resulted in a well-supported hypothesis that "low plasma concentration of essential fatty acids is associated with depression" (Williams et al., 2006, p. 117). Among numerous completed studies, Williams et al. (2006) found that omega-3 supplementation was positively correlated with significantly longer periods of remission between depressive episodes. Additionally, a study investigating various doses of EPA found that depressed adults receiving one gram (1000 mg) of EPA per day demonstrated significant improvement over placebo, despite continued treatment with medication (Williams et al., 2006). Williams et al. (2006) also reported on another study which assessed the efficacy of omega-3s in the treatment of depression and found that omega-3s used in combination with conventional antidepressant treatment resulted

DISCUSSION

As increasing numbers of MDD sufferers turn to CAM for treatment, it behooves those working within the health services to learn more about CAM therapies, specifically with an eye for those that have the greatest record of clinical efficacy. In the treatment of MDD, the nutritional supplements SAMe and omega-3 fatty acids should certainly be considered. Studies have shown that both SAMe and omega-3s have been used to successfully mitigate the symptoms of chronic depression and, in some cases, to prolong remission between episodes. Unfortunately, the heterogeneity of the studies has not produced clinical measures regarding proper dosages of these two supplements for MDD patients. In part, this may be due to the difficulty of ascribing cause-and-effect relationships where aspects of nutrition are concerned. As Sarris et al. (2009) suggested, "Attempting to create a physiological change via the prescription of a single nutrient is ambitious, given the complex nature of other nutritional intake and of internal biochemical mechanisms" (p. 125). The study of nutrition, after all, is a study of synergistic effects.

SAMe presents a good example, as its synthesis "relies, in part, on adequate concentrations of the vitamins folate

in more rapid clinical improvement, even in treatment-resistant, severely depressed individuals.

Interestingly, a review of the literature indicates that studies are mixed on whether DHA or EPA is most significantly related to the treatment of depression. One study found lower levels of plasma EPA in depressed individuals; another indicated that DHA levels in red blood cells were much lower in depressed people than in non-depressed (Milte et al., 2009). Surveying various available studies suggests the therapeutic range of omega-3 supplementation falls between approximately 1000-6000 mg/day, using a combination of both DHA and EPA to meet those amounts. No adverse effects were noted in any of the studies mentioned.

References

Blakaj, D. M. (2010). A mini analysis: Depression and omega-3 essential fatty acids. Einstein Journal of Biology & Medicine, 25, 2633-35.

Higdon, J. (2005). Essential fatty acids. Linus Pauling Institute – Oregon State University. Retrieved from http://lpi.oregonstate.edu/infocenter/othernuts/omega3fa/

Logan, A. C. (2006). Omega-3 fatty acids and depression. Positive Health, 127, 24-29. Retrieved from EBSCOhost.

Milte, C., Sinn, N., & Howe, P. (2009). Polyunsaturated fatty acid status in attention deficit hyperactivity disorder, depression, and Alzheimer's disease: towards an omega-3 index for mental health? Nutrition Reviews, 67(10), 573-590. Retrieved from EBSCOhost.

Mindell, E. (2004). Earl Mindell's new vitamin bible (4th ed.). New York, NY: Warner Books.

Mischoulon, D., & Fava, M. (2002). Role of S-adenosyl-L-methionine in the treatment of depression: A review of the evidence. American Journal of Clinical Nutrition, 76(5):1158S–61S.

Office of Dietary Supplements (ODS). (2005). Omega-3 fatty acids and health. Retrieved from http://ods.od.nih.gov/factsheets/Omega3FattyAcidsandHealthSarris, J., Schoendorfer, N., & Kavanagh, D. J. (2009). Major depressive disorder and nutritional medicine: a review of monotherapies and adjuvant treatments. Nutrition Reviews, 67(3), 125-131. Retrieved from EBSCOhost.

Tippens, K., Marsman, K., & Zwickey, H. (2009). Is prayer CAM? The Journal of Alternative and Complementary Medicine, 15(4), 435-438.

White, K. P. (2009). What psychologists should know about homeopathy, nutrition, and botanical medicine. Professional Psychology: Research and Practice, 40(6), 633-640. doi:10.1037/a0016051

Williams, A. L., Katz, D., Ali, A., Girard, C., Goodman, J., & Bell, I. (2006). Do essential fatty acids have a role in the treatment of depression? Journal of Affective Disorders, 93(1-3), 117-123.

Zurfluh, R., & Shapses, S. (2008). Fat intake. Encyclopedia of Obesity. Retrieved from http://0-www.sage-ereference.com.leopac.ulv.edu/obesity/Article_n166.html

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and B-12" (Mischoulon & Fava, 2002, p. 1158S). Without assessing a patient's levels of these two nutrients, treatment with SAMe may fail or have minimal effect. Another area of concern for the use of SAMe is the form in which it is utilized. Typically administered via injection, SAMe is more commonly available in tablet form, and while it is easily found in health food stores across the nation, costs may be prohibitive, especially as insurance companies typically do not cover these treatments (Mischoulon & Fava, 2002).

There remain questions about the proper use of omega-3s, as well. Research has yet to discern precise clinical dosages and "the total amount of omega-3 fatty acids in fish oil is highly variable" (Blakaj, 2010, p. 34); a range of 1000-6000 mg/day may mean the difference between as many as one to twelve large capsules with varying combined doses of both DHA and EPA. Additionally, widely available OTC omega-3 supplements contain EFAs from different sources including herbs, seeds, and fish. Most omega-3 studies use EFAs derived from fish oils, which may expose patients to toxins such as PCBs and mercury; distillation of fish oils is essential for product purity (Mindell, 2004). Plant sources of omega-3s (i.e., nuts and seeds) do not yield EPA directly; an algae-based supplement can yield DHA and alpha-linolenic acid (ALA), from which EPA can be synthesized, but such synthesis "may be insufficient under certain conditions" (Higdon, 2005, para. 4). This makes omega-3 supplementation with fish oils most appropriate for clinical use and simultaneously problematic for some members of the population (i.e., vegetarians and vegans). Yet supplementation with omega-3s may be specifically useful as a treatment option for populations that cannot use standard medications, such as pregnant women. Research has indicated that omega-3s significantly reduce depression in pregnant patients, without placing the developing fetus in any harm (Sarris et al., 2009). Indeed, as omega-3s are required for proper fetal brain development, supplementing with them may protect pregnant women from deficiency and, thereby, depression.

CAM approaches to depression are many; this paper proposed only two. Additional studies will be necessary to establish recommendations for the clinical use of SAMe and omega-3s. Until that time, patients may achieve benefit from supplementing with both nutritional supplements at dosages established in conjunction with a physician's knowledge and advice.