Complementary and Alternative Therapies for Common Health Conditions

Stacey Littlefield

American College of Healthcare Sciences

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The use of complementary and alternative medicine (CAM) continues to gain in popularity in the United States. According to Clarke et al. (2015), nearly 34% of American adults aged 18 and over use complementary health approaches. These health approaches are not limited to adults. Black et al. (2015), report that nearly 12% of children aged four to 17 years use or have been provided with CAM treatments. For the past 11 years, sales of herbal medicines in the United States have risen over the previous year, with nearly $6.4 billion spent on herbal supplements in 2014 alone (Smith et al., 2015). These figures suggest a clear trend that Americans are continuing to turn to CAM treatment for their health concerns and well-being.

Among both adults and children, the most common CAM therapies include: natural products other than vitamins and minerals, yoga, Tai Chi or Qi Gong, deep breathing, chiropractic manipulation and meditation (Black et al., 2015; Clarke et al., 2015). Individuals turn to these CAM treatments to treat health conditions when conventional therapies have failed or when the risks of those therapies outweigh the benefits (Stussman et al., 2015). Depression, anxiety, and attention-deficit hyperactivity disorder (ADHD) are some of the most common mental health disorders in the United States (CDC, 2015; CDC, 2011; NIMH, n.d.). These complex disorders affect tens of millions of children and adults annually. Furthermore, depression and anxiety often co-occur with other problems, such as chronic pain, which affects 25.3 million American adults. These common health conditions involve conventional treatments with severe side effects, including addiction to opioid pain medications, sexual dysfunction with antidepressants and sleep disturbances with ADHD medication. Moreover, a significant percentage of individuals suffering with these conditions do not respond to the available pharmaceutical treatments. For example, 20% to 35% of children with ADHD are non-
responders, and surprisingly, antidepressants seem to show efficacy in only 40% of patients (Esparham, Evans, Wagner & Drisko, 2014; Geddes et al., 2003). According to Nahin, Stussman & Herman (2015), people suffering from back, neck, joint pain and arthritis spend roughly $14 billion out-of-pocket on CAM treatments.

As the popularity of CAM therapies grow, so grows the need for education on these CAM options. Given the large percentage of the United States population using CAM therapies, paired with the percentage of individuals who do not respond to current pharmaceutical options, it can be expected that millions of people suffering with pain, ADHD, anxiety and depression are actively pursuing alternative health approaches. An expanding body of scientific research continues to investigate various modalities and continues to confirm their benefits. Mind-body therapies, such as yoga and meditation have been applied in pain management and have been found to reduce chronic pain (NCCIHb). Furthermore, more evidence regarding the impact of stress on chronic pain supports the integration of mind-body therapies, which are known to reduce the negative effects of stress. Acupuncture, a vital component of Traditional Chinese Medicine has also been shown to be effective for various types of chronic pain (NCCIHb). Dietary interventions for ADHD, first introduced in the 1970’s with the Feingold Diet are now recognized as relevant and impactful in the management of ADHD symptoms (Millichap and Yee, 2012). In addition, strong evidence exists that exposure to pesticides increases ADHD risk, which supports a diet rich in organically-grown foods. Supplementation with nutrients, including omega-3 fatty acids and herbal medicines has also shown promise (Millichap and Yee, 2012). CAM therapies also have positive benefits in anxiety and depression; dietary interventions, supplemental nutrients and botanicals such as St. John’s wort have been used historical and have been proven in clinical research (Gaby, 2011; Linde et al., 2008).
scientific literature available shows that CAM therapies are viable therapeutic options for pain management, ADHD, anxiety and depression.

**Methods**

The CDC website was searched to collect statistical information on the rates of ADHD, anxiety and depression and chronic pain. The National Institute of Mental Health (NIMH) was also searched for statistical information on current treatments for anxiety, depression and ADHD. The National Center for Complementary and Integrative Health (NCCIH) was searched for statistical information of the use of CAM therapies in the United States and for which conditions they were most used. The NCCIH website also included basic information on various types of CAM therapies. The American Botanical Council website was referenced for information regarding botanical treatments for anxiety, depression, ADHD and pain management.

The following databases were searched using several Boolean search terms: Pubmed, Google Scholar, Deepdyve and ReadCube. The Boolean search terms included: “pain AND complementary”; “pain AND acupuncture”; “pain AND stress”; “pain AND yoga”; “pain AND meditation”; “pain AND Traditional Chinese Medicine”; “pain AND botanical”; “pain AND turmeric”; “pain AND boswellia”; “headache AND acupuncture”; “joint AND turmeric”; “joint AND boswellia”; “stress AND herbal”; “joint AND natural”; “pain AND vitamin D”; “pain AND omega-3”; “ADHD AND diet”; “ADHD AND pesticides”; “ADHD AND polyunsaturated fats”; “ADHD AND complementary”; “ADHD AND theanine”; “ADHD AND herbal”; “ADHD AND botanical”; “anxiety AND depression AND diet”; “anxiety AND depression AND complementary”; anxiety AND depression AND magnesium”; anxiety AND depression AND folate” “depression AND vitamin B12”; “depression AND omega-3”; anxiety AND depression AND herbal”; “anxiety AND depression AND botanical”.
Results

Pain Management

According to NICCH (2015a) back, neck and joint pain, headache and migraine are the most common types of pain; in addition, back pain is the most frequent reason why individuals try CAM therapies (Ernst, 2004). Jennings, Okine, Roche & Finn (2014) state that exposure to both acute and chronic stress can aggravate clinical pain conditions; furthermore, repeated and chronic stress produce changes in neurological pain pathways which result in a phenomenon known as stress-induced hyperalgesia. This phenomenon was studied in healthy female subjects and fibromyalgia patients. Both groups experienced enhanced pain sensitivity to a thermal stimulus following a psychological stressor; however, only fibromyalgia patients experienced enhanced pain sensitivity to pressure pain (Crettaz et al., 2013). The authors theorized that the underlying mechanisms involved in the response to stress may be different in those with chronic pain (Crettaz, et al., 2013).

Chronic pain patients often show dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, as major component of the neuroendocrine system that controls stress (Vachou-PRESSAU et al., 2013). The allostatic load, resulting from adaptation to repeated stress, can lead to an over-activation of the HPA axis and increased levels of glucocorticoids, which causes changes in the hippocampal region (Vachou-PRESSAU et al., 2013). A study of 16 patients with chronic back pain and 18 healthy subjects serving as control examined cortisol levels, hippocampal volumes and brain activation to thermal stimuli. The results demonstrated that the subjects with chronic back pain had higher levels of cortisol than the control group (Vachou-PRESSAU et al., 2013). The higher cortisol levels in these patients were correlated with decreased hippocampal volume and increased brain activity evoked by pain (Vachou-PRESSAU et al., 2013).
Acupuncture. The German Acupuncture Trials (GERAC) compared true acupuncture with sham acupuncture and conventional therapy in subjects with chronic low back pain. The trial was patient and observer-blinded, randomized and controlled and involved 1,162 patients with a history of chronic low back pain for an average of eight years. Subjects went through ten 30-minute session of true acupuncture according to the practice of Traditional Chinese Medicine; sham acupuncture, which involved superficial needling at non-acupuncture points; or a combination of nonsteroidal anti-inflammatory drugs and/or pain medication, physical therapy and exercise (Haake, et al., 2007). At six months, the response rate in the true acupuncture group was 47.6%, 44.2% in the sham acupuncture group, and 27.4% in the conventional therapy group. The effectiveness of acupuncture was nearly twice that of conventional therapy (Haake, et al., 2007). The authors note that although there was little difference between the true and sham acupuncture groups, the benefits could not be solely attributed to the placebo effect. Rather, they theorize that acupuncture has specific effects not yet understood which are independent of needle placement and depth that lead to symptomatic improvement (Haake, et al., 2007).

Brinkhaus et al. (2006) conducted a randomized controlled trial to investigate whether acupuncture was more effective in reducing pain than minimal acupuncture or no acupuncture in subjects with chronic low back pain. Minimal acupuncture served as the sham treatment. According to the authors, the waiting list control group was included due to the fact that sham acupuncture may not be a “physiological inert placebo” (Brinkhaus et al., 2006). Both acupuncture groups received 12-30 minute sessions over 8 weeks; a total of 298 subjects were included in the trial. At week eight, pain intensity decreased from baseline by a mean ± SD of 28.7 ± 30.3 mm in the acupuncture group, 23.6 ± 31.0 mm in the sham acupuncture group, and 6.9 ± 22.0 mm in the waiting list group. Fifty four percent of the acupuncture group had at least
a 50% reduction in pain, compared with 38.6% in the sham acupuncture group and 14.9% in the waiting list group. The researchers concluded that acupuncture was more effective than no acupuncture for chronic low back pain.

Vickers et al. (2012) conducted a meta-analysis of individual patient data of acupuncture for chronic pain. The authors used data from 29 eligible RCTs, with a total of 17,922 patients. The RCTs included in the meta-analysis investigated a variety of chronic pain conditions, including: musculoskeletal pain, chronic headache, osteoarthritis, back pain, and neck pain (Vickers et al., 2012). Based on these studies, the authors found statistically significant differences between acupuncture vs. sham acupuncture and between acupuncture vs. a no-acupuncture – waiting list control for all types of pain reviewed (Vickers et al., 2012). Patients who received true acupuncture had less pain (Vickers et al., 2012). They concluded that acupuncture is superior to control and sham acupuncture for chronic pain; therefore, acupuncture is a reasonable treatment option for chronic pain (Vickers et al., 2012).

Acupuncture has also proven efficacious for tension-type headaches (Linde et al., 2011b). Tension-type headaches occur on both sides of the head with episodes of pressing or tightening pain. In some individuals tension-type headaches can become chronic, occurring 15 or more days per month. A Cochrane Review investigated whether acupuncture is more effective than no preventative treatment or routine care only; sham acupuncture; or as effective as other treatments in reducing headache frequency in patients with episodic or frequent tension-type headache (Linde et al., 2011b). Eleven trials with a total of 2,317 subjects met the inclusion criteria for the review. Two trials were large and examined the addition of acupuncture to routine care. In these trials, a total of 47% of patients receiving acupuncture reported a decrease in the total number of headache days by at least 50%; only 16% of patients in control groups reported such changes.
(Linde et al., 2011b). Six trials compared true acupuncture to sham acupuncture; these trials demonstrated slightly better results in the true acupuncture groups, with 50% of patients receiving true acupuncture reporting a declining number of headache days by 50%, compared to 41% of patients in the sham groups (Linde et al., 2011b). Linde et al. (2011b) updated a previous version of this Cochrane Review by concluding that acupuncture could be valued as a non-pharmacological treatment for frequent or chronic tension-type headache.

Another Cochrane Review examined acupuncture as a prophylactic treatment for migraine. Linde et al. (2011a) included 22 trials with 4,419 subjects in their review. Six trials compared acupuncture to routine care only or no preventative treatment. The results of these trials showed that patients in the acupuncture group had lower headache scores, fewer headache days and frequency and greater response rates (Linde et al., 2011a). Furthermore, one of these six studies conducted long-term follow up that demonstrated patients who received acupuncture were significantly better than those receiving routine treatment nine months after completion of treatment (Linde et al., 2011a). The four trials comparing acupuncture to proven prophylactic drug treatment indicated that acupuncture had slightly better outcomes; however, the acupuncture group experienced significantly fewer adverse events (Linde et al., 2011a). The authors concluded their review suggested that acupuncture was as effective as and possibly better than prophylactic drug treatment (Linde et al., 2011a).

**Mind-body techniques.** National Health Interview Surveys show the practice of yoga as a CAM therapy has steadily increased from 2002 to 2012 (Clarke et al., 2015). Yoga as a means for pain management is an ancient practice originating in India and is currently recommended by the American Pain Society’s guidelines on the treatment of low back pain (Chou et al., 2007).
Several clinical studies have been conducted on yoga’s impact on pain and several reviews and meta-analyses have look at the clinical evidence.

Wren, Wright, Carson and Keefe (2011) reviewed studies that demonstrate the potential role of yoga in pain management for a variety of conditions, including carpal tunnel syndrome, osteoarthritis and fibromyalgia. In the study investigating carpal tunnel syndrome, 42 patients experiencing pain were assigned to either an Iyengar yoga program or control, which was a wrist splint. When compared to the control group, the yoga group demonstrated significant reductions in pain; moreover, their grip strength increased (Wren et al., 2011). The same group of researchers also investigated yoga in osteoarthritis (OA) of the hand and garnered results similar to the carpal tunnel trial. The yoga group in the OA study showed significant improvements in pain during activity (Wren et al., 2011). The authors of the review included a small controlled pilot study on yoga for fibromyalgia patients. The subjects were assigned to an eight week yoga program or to wait-listed standard care, which served as a control. The yoga group exhibited significant improvements in outcomes which included pain (Wren et al., 2011).

Bussing, Ostermann, Ludtke and Michalsen (2012) conducted a meta-analysis on the effects of yoga on pain and associated disability. A total of 16 studies examining back pain, rheumatoid arthritis, headache or migraine and other indications were included in the meta-analysis. Five studies were randomized and single-blinded; seven studies were randomized with no blinding; and four were non-randomized. Four studies described strong effects of yoga on pain frequency and intensity and six studies reported moderate effects (Bussing et al., 2012). The authors concluded that yoga was useful as a supportive intervention for many pain-associated diseases and that larger scale trials should be conducted to further study their findings (Bussing et al., 2012).
A systematic review and meta-analysis examined yoga specifically for low back pain (LBP). Cramer, Lauche, Haller and Dobos (2013) included 10 randomized trials with a total of 967 chronic low back pain patients. The studies used various styles of yoga, including Iyengar yoga, Hatha yoga and Viniyoga; two studies did not specify the style of yoga. Meta-analysis demonstrated strong evidence for the short-term effects of yoga on LBP compared to controls. At long-term follow up, there was moderate evidence for reduction of LBP (Cramer et al., 2013).

Meditation has the ability to alter sensory, cognitive and affective processes of a person’s subjective experience. Mindfulness meditation refers to a specific subfamily of meditation techniques derived from Buddhist traditions (Eberth & Sedlmeier, 2012). This type of meditation is used to develop mindfulness: the self-regulation of a person’s attention to the awareness of his or her immediate experiences while cultivating openness and acceptance (Eberth & Sedlmeier, 2012). Several studies have shown that mindfulness meditation can attenuate the subjective experience of pain (Zeidan et al., 2011). One randomized controlled trial investigated the impact of mindfulness meditation in chronic pain. One hundred and nine patients with nonspecific chronic pain were randomly assigned to a mindfulness meditation program or to a wait-list control (la Cour & Petersen, 2015). Measurements included mental function, physical function, pain, and pain acceptance and quality of life; the SF 36 Vitality Scale was used as the primary outcome measure. The participants attended weekly group meetings, eight of which were three hour sessions and of which was 4.5 hours. Participants were also taught to meditate daily for 45 minutes at home. The results of the study showed a significant effect on the SF36 Vitality Scale; in addition, significant effects were found for lower depression and anxiety, better control of pain and higher pain acceptance (la Cour & Petersen, 2015). These effects were also seen at a six month follow up (la Cour & Petersen, 2015). The authors
concluded that mindfulness meditation had positive contributions to pain management and can have positive benefits on other dimensions of chronic pain, including anxiety and depression (La Cour & Peterson, 2015).

Another study highlights the benefits of mindfulness meditation in an older population with chronic low back pain (CLBP). Morone, Greco and Weiner (2008) conducted a pilot study, as a randomized controlled clinical trial to assess an eight session mindfulness meditation program. Thirty-seven older adults, aged 65 and older with daily moderate CLBP were randomized to the eight week program or a wait-list control. Quality of life, physical function, pain and attention were assessed at baseline, eight weeks, and at three month follow-up. Eighty one percent of participants completed the eight week assessments. Participants meditated an average of 4.3 days a week at an average 31.6 minutes per day (Morone et al., 2008). Results, when compared to control, demonstrated the meditation group experienced significant improvement in Chronic Pain Acceptance Questionnaire Total Score and Activities Engagement subscale and SF-36 Physical Function (Morone et al., 2008). The three month follow-up showed sustained benefit (Morone et al., 2008). The authors concluded a mindfulness meditation program is feasible for older adults with CLBP, and consider such a program as a promising non-pharmacologic adjunct to pain treatment (Morone et al., 2008).

**Botanicals.**

**Antinociceptive and analgesic.** Plants have served as analgesics for thousands of years, particularly in the Ayurvedic and Traditional Chinese systems of medicine. One such herbs is *yan hu suo*, (*Corydalis yanhusuo*), used in several Traditional Chinese herbal formulas for pain. Promising preliminary studies on corydalis show antinociceptive and analgesic effects. Choi et al. (2012) examined these effects using a chronic constriction injury-induced neuropathic pain rat
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model. In a thermal hyperalgesia test, corydalis produced significant antinociception; furthermore, corydalis was shown to significantly decrease nerve injury-induced allodynia (Choi et al., 2012). The authors theorize the antinociceptive effects may be produced by prevention of phosphorylation of the NRI subunit on the NMDA receptor (Choi et al., 2012).

Zhang et al. (2014) investigated the specific compounds in corydalis responsible for the tuber’s analgesic properties. Dehydrocorybulbine (DHCB) was identified and isolated from corydalis. Various tests conducted in mice showed that DHCB exhibits dose-dependent antinociceptive effects and anti-inflammatory effects. In addition, DHCB was shown to exert its effects through dopamine D₂ receptors, not the µ opioid receptor. Tolerance tests in mice demonstrated that DHCB did not cause tolerance, unlike morphine.

Ashwagandha (*Withania somnifera*) is one of the most revered plants in Ayurveda. It is commonly used to treat many different diseases and is often included as an ingredient in formulations for osteoarthritis and rheumatism (Engels & Brinckmann, 2013). Nalini, Manjunath, Reddy and Usharani (2013) set out to elucidate the possible analgesic activity of ashwagandha using the Hot Air Pain Model in healthy volunteers. The participants were given either two 500mg capsules of ashwagandha or placebo with water. The results of this study showed that a single 1,000 mg dose of ashwagandha significantly increased Pain Threshold Time when compared to baseline measurements and placebo (Nalini, 2013).

**Anti-inflammatory.** Both turmeric (*Curcuma longa*) and boswellia (*Boswellia serrata*) have been studied for their anti-inflammatory benefits in pain conditions such as osteoarthritis. The active constituents in turmeric, the curcuminoids, have established protective benefits on chondrocytes (Gupta, Patchva & Aggarwal, 2013). Panahi et al. (2014) investigated the efficacy of curcuminoids in osteoarthritis. Forty subjects participated in a six week randomized, double-
blind, placebo-controlled trial. Nineteen participants were assigned to the curcuminoids group and 21 to the placebo group. The treatment group used 1,500 mg of C³ Complex daily, in three divided doses. The primary outcome measure was the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC). Severity of pain was assessed using VAS and Lequesne’s pain functional index (LPFI). The curcuminoids group experienced greater reductions in WOMAC, VAS, and LPFI scores compared to placebo. In the WOMAC subscales specifically, there were significant improvements in the pain score (Panahi et al., 2014).

Meriva, a curcumin-phosphatidylcholine phytosome complex has been studied in two clinical trials for osteoarthritis. The first study involved 50 patients evaluated for the symptoms of osteoarthritis with the WOMAC scale and overall anti-inflammatory response was measured by plasma concentration of C-reactive protein (CRP). The participants were divided into two groups, one receiving 1g of Meriva in two doses or “the best available treatment” (Belcaro, et al., 2010a). After three months, the Meriva group experienced a 58% reduction in the global WOMAC score and CRP levels were significantly decreased (Belcaro et al., 2010a). A second study on Meriva investigated the long-term efficacy and safety in an eight month study on 100 patients with osteoarthritis. This study was methodologically similar to the smaller trial; however, a wider series of inflammatory markers were evaluated, including IL-1β, IL-6, sCD40L, sVCAM-1 and ESR (Belcaro et al., 2010b). The results of this larger study showed the treatment group had a 50% reduction in WOMAC scores. The inflammatory markers were also significantly decreased (Belcaro et al., 2010b).

*Boswellia serrata* also enjoys positive studies in OA. In a 2008 study, 5-Loxin, a boswellia extract enhanced with 30% 3-O-acetyl-11-keto-beta-boswellic acid (AKBA) was examined in a three month RCT for OA. Seventy five participants received 100mg or 250mg 5-
Loxin daily or placebo. WOMAC and LFPI were used as outcome measurements; in addition, metalloproteinase-3, a cartilage degrading enzyme matrix was also evaluated (Sengupta et al., 2008). At the trial’s end, both 100mg and 250mg doses of 5-Loxin demonstrated statistically significant improvements in WOMAC and LFPI scores (Sengupta et al., 2008). Furthermore, at the higher dose, 5-Loxin showed improvement in pain scores at the seven day mark (Sengupta et al., 2008). Significant reductions in metalloproteinase-3 were also recorded (Sengupta et al., 2008). Vishal, Mishra and Raychaudhun (2011) investigated Aflapin, a boswellia extract standardized for 20% AKBA and non-volatile oil. Sixty patients participated in this RCT and were randomly assigned to receive 50mg Aflapin twice daily or placebo for 30 days (Vishal et al., 2011). All patients were assessed using WOMAC. The results of this study demonstrate a significant reduction in WOMAC scores of nearly 50 percent (Vishal et al., 2011). Pain, joint stiffness and physical discomfort were all reduced in the treatment group (Vishal et al., 2011).

Adaptogens. As a unique class of herbal medicines, adaptogens increase resistance against various stressors in a non-specific fashion, thereby reducing stress-induced disorders and impairments of the neuroendocrine system (Panossian and Wagner, 2011). Rhodiola rosea and Withania somnifera are both considered adaptogens with several documented pharmacological activities. Several studies on Rhodiola rosea demonstrate its stress-protective effects. These studies show that R. rosea reduces the activation of various components of the stress response system (Panossian and Wagner, 2011). For example, reduction in the secretion of corticotrophin releasing factor provides a protective effect on the CNS; furthermore, modulation of the HPA axis reduces subsequent damage from stressors (Brown, Gerbarg, Ramazanov, 2002).

In a randomized, double-blind, placebo controlled trial on 98 chronically stressed patients, Auddy et al. (2008) investigated the effect of a standardized Withania somnifera extract
(WSE) on several stress-related parameters. Patients were randomized into four groups: WSE 125 mg QD, WSE 125 mg BID, WSE 250 mg BID and placebo. Biomarkers of stress, including serum concentrations of cortisol, dehydroepiandrosterone sulfate (DHEAS) and CRP were measured from blood samples (Auddy et al., 2008). Results showed the WSE 125 mg QD group experienced statistically significant reductions in serum cortisol and CRP, pulse rate and blood pressure, and an increase in serum DHEAS (Auddy et al., 2008).

**Supplemental nutrients.**

**Vitamin D.** Emerging research on vitamin D suggests its role in human health extends beyond healthy bones. Vitamin D deficiency has been associated with several pain states, including fibromyalgia, headache, back pain and persistent musculoskeletal pain (Shipton and Shipton, 2015). Long-term deficiencies in vitamin D have also been linked to chronic inflammation, which can lead to many health conditions characterized by pain as a disabling symptom (Shipton and Shipton, 2015). Vitamin D plays several roles in the pain process, particularly those involved in neuropathic pain. For example, vitamin D modulates brain neurotransmitters, such as dopamine, acetylcholine and serotonin. In addition, it modulates neuronal excitability by affecting neurotransmitter receptors including GABA and NMDA (Shipton and Shipton, 2015).

Huang et al. (2005) evaluated vitamin D supplementation in patients with multiple areas of chronic pain. Participants included 28 U.S. veterans with low serum levels of 25-hydroxyvitamin D [25(OH)D] and chronic pain. If serum 25(OH)D was deemed insufficient, participants supplemented with 1,200 IU vitamin D daily; if serum 25(OH)D was found to be deficient, participants were given 5,000 IU weekly (Huang et al., 2005). Pain was assessed by the zero to 10 pain score and the Veterans Rand 36 (VR-36) bodily pain domain score.
Significant improvements were seen in the pain score and in bodily pain (Huang et al., 2005). After vitamin D supplementation, the percentage of participants with greater than three pain areas decreased to 53.6% from 64.3% (Huang et al., 2005). Their mean pain score decrease to 5.68 from 7.11 and their bodily pain assessed by VR-36 improved to 63.4 from 27.04 (Huang et al., 2005).

**Omega-3 fatty acids.** Omega-3 fatty acids, generally taken as fish oil, have been used to treat joint pain associated with various inflammatory conditions. Goldberg and Katz (2007) conducted a meta-analysis to examine the effectiveness of omega-3 polyunsaturated fatty acids ($\omega$-3 PUFAs) in alleviating joint pain associated with rheumatoid arthritis, dysmenorrhea and inflammatory bowel disease. Seventeen studies with 823 participants were included in the meta-analysis. The majority of studies used fish oil supplements; one study used krill oil and one study used flax oil (Goldberg and Katz, 2007). Total $\omega$-3 PUFA supplementation ranged from 1.7 g to 9.6 g daily (Goldberg and Katz, 2007). In studies conducted for three to four months, statistically significant differences were demonstrated for patient-assessed pain, morning stiffness and the number of painful and/or tender joints between the treatment and placebo groups and in favor of $\omega$-3 PUFAs (Goldberg and Katz, 2007). In studies five months or longer, statistically significant differences in favor of $\omega$-3 PUFAs were seen for physician-assessed pain and the number of painful and/or tender joints (Goldberg and Katz, 2007). The authors concluded that supplementing with $\omega$-3 PUFAs for at least three months improved joint pain associated with said conditions (Goldberg and Katz, 2007).

Omega-3 polyunsaturated fatty acids were also investigated in adolescents with recurrent migraines. This study included 27 adolescents suffering from frequent migraines for at least one year (Harel et al., 2002). The study design was a randomized, double-blind, cross-over study
with two months of fish oil, a one month wash-out and two months of placebo, which was olive oil (Harel et al., 2002). Severity and duration of migraines were self-assessed using 7 point faces and 10 point visual analog pain scales and 5 point frequency and severity rating scales (Harel et al., 2002). Twenty three patients completed the study. When frequency was compared before and after the study, there was a significant reduction during fish oil treatment. This effect was also seen in headache severity (Harel et al., 2002). Eighty seven percent of participants experienced a reduction in the frequency of headaches and 83% had a reduction in severity (Harel et al., 2002). Seventy four percent had a reduction in duration with fish oil (Harel et al., 2002). These results were considered marked improvements from baseline (Harel et al., 2002). Interestingly, there were not significant differences between fish oil and olive oil; however, the authors concluded that these results should not be dismissed (Harel et al., 2002). Rather, the results demonstrated the possibility that olive oil may not have been an inert placebo (Harel et al., 2002).

Attention Deficit – Hyperactivity Disorder (ADHD)

**Dietary Interventions.**

*Restricted elimination diet (RED).* The Impact of Nutrition in Children with ADHD (INCA) study conducted in the Netherlands on 100 children ages four to eight years, consisted of an open label phase followed by a double-blind crossover challenge phase. In the open label phase, weeks one to three served as the baseline period; 50 children continued their normal diet and parents received healthy diet advice (Pelsser et al., 2011). The other 50 children began the RED, consisting of mainly rice, meat, vegetables, pears and water, complemented with fruits, potatoes and wheat (Pelsser et al., 2011). At the end of the second week, 17 of the children in the RED group had no behavioral response so their diets were restricted further to meat, rice,
vegetables, pears and water (Pelsser et al., 2011). By the end of phase I, symptoms of ADHD significantly improved on the abbreviated Conner’s scale by 11.6 in 64% of children in the RED group compared to no improvement in the control group (Pelsser et al., 2011). Children in the RED group who experienced a clinical response in phase I moved forward to phase II, the double-blind crossover food challenge. In this phase, a relapse of ADHD symptoms occurred in 63% of children (Pelsser et al., 2011).

An earlier trial of 76 hyperactive children examined the effect of an oligoantigenic diet for four weeks. The diet consisted of two meats (lamb and chicken), two carbohydrates (potatoes and rice) and two fruits (banana and apple), any brassica vegetable, water, vitamins and calcium (Egger, Graham and Carter, 1985). Eighty two percent or 62 children improved and behavior was deemed normal in 21 children (Egger, Graham and Carter, 1985). Twenty eight children who improved proceeded to a double-blind placebo controlled crossover trial in which they received food challenges. Symptoms relapsed or worsened more often when children were given suspected allergenic foods over placebo (Egger, Graham and Carter, 1985). Sixty four percent of children reacted to milk, 49% reacted to wheat and 32% reacted to peanuts (Egger, Graham and Carter, 1985).

Nigg, Lewis, Edinger and Falk (2012) conducted a meta-analysis of REDs in ADHD or ADHD symptoms. The analysis included 14 open label trials and 16 controlled trials on children with ADHD with a total of 2,220 children. A significant effect size of 0.29 was found and the authors concluded that REDs indeed improve ADHD symptoms in about 30% of hyperactive children (Nigg et al., 2012).

McCann et al. (2007) investigated whether consumption of artificial food colors and additives (AFCA) affected childhood behavior. One hundred fifty three, three-year-old and 144
eight to nine year old children from the general population not specifically diagnosed with ADHD were included in a randomized, double-blind, placebo controlled trial. The children were challenged with a drink containing a mix of AFCA plus sodium benzoate or placebo. For the three year olds, mix A included 20 mg of AFCA and 45 mg sodium benzoate; mix B contained 30 mg of AFCA and 45 mg sodium benzoate (McCann et al., 2007). For the eight and nine year olds, mix A contained 24.98 mg AFCA and 45 mg sodium benzoate; mix B contained 62.4 mg AFCA and 45 mg sodium benzoate (McCann et al., 2007). Prior to the drink challenge, the AFCA to be used in the study and sodium benzoate were removed from the children’s diets for six weeks (McCann et al., 2007). A global hyperactivity aggregate, based on observed behaviors and ratings by teachers and parents, plus for eight and nine year olds, the Conner’s Continuous Performance Test II (CPTII) was used as the main outcome measure. The results demonstrated that mix A had significant adverse effects on GHA compared to placebo (McCann et al., 2007). The authors concluded that food additives adversely affect hyperactivity in three year old and eight and nine year olds (McCann et al., 2007).

**Pesticides.** The association between organophosphate (OP) exposure and ADHD was investigated by Bouchard, Bellinger, Wright and Weisskopf (2010). The researchers used data from the National Health and Nutrition Examination Survey (2000-2004) and isolated 119 children ages eight to 15 years who met the diagnostic criteria for ADHD. Urine samples were tested for six urinary dialkyl phosphate (DAP) metabolites, markers of OP exposure (Bouchard et al., 2010). Based on their statistical analysis of the data, Bouchard et al. (2010) determined that children with higher concentrations of DAPs in urine, particularly dimethyl alkylphosphates (DMAP) had increased odds of meeting DISC-IV criteria of ADHD. The most common DMAP
detectable in children, dimethylthiophosphate was associated with double the odds of ADHD when the concentrations were above the median of detectable limits (Bouchard et al., 2010).

Wagner-Schuman et al. (2015) used data from eight to 15 year old participants in the 2001-2002 National Health and Nutrition Examination Survey to assess the association between pyrethroid exposure and ADHD. A total of 687 participants’ data were included. Pyrethroid exposure was determined by urinary levels of the pyrethroid metabolite 3-phenoxybenzoic acid (3-PBA) (Wagner-Schuman et al., 2015). ADHD was defined by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition or by caregiver report of a previous diagnosis. The results of this study showed that children with detectable levels of 3-PBA were twice as likely to have ADHD as those with undetectable levels (Wagner-Schuman et al., 2015). Furthermore, for every 10-fold increase in 3-PBA levels, hyperactive-impulsive symptoms increased by 50% (Wagner-Schuman et al., 2015). These associations were also sex-specific, being significant in boys compared to girls (Wagner-Schuman et al., 2015).

**Supplemental nutrients.**

**Polyunsaturated fatty acids.** Bloch and Qawasmi (2011) conducted a systematic review and meta-analysis to explore the efficacy of supplementing omega-3 fatty acid in children with ADHD. Ten trials with 699 children were included in the meta-analysis. These trials ranged in seven weeks to four months and utilized varying omega-3 fatty acid supplements with EPA dosages from zero to 750 mg and DHA dosages from 95 mg to 2.7 g (Bloch and Qawasmi, 2011). Bloch and Qawasmi (2011) reported a small but significant benefit of omega-3 fatty acid supplementation in ADHD. In analyzing these studies, the authors found a significant association between EPA dosage and efficacy (Bloch and Qawasmi, 2011). They concluded that based on the benign adverse events and modest efficacy, omega-3 fatty acid supplementation
was reasonable augmentation of pharmaceutical treatment or for families who choose not to use pharmaceutical interventions (Block and Qawasmi, 2011).

A phosphatidylserine – omega 3, EPA enriched product was studied for its efficacy in ADHD (Manor et al., 2012). Two hundred children with ADHD participated in a 15-week double-blind, placebo controlled trial followed by a 15-week open label extension. The Conner’s parent and teacher rating scale (CRS-P,T), Strength and Difficulties and Questionnaire (SDQ) and Child Health Questionnaire (CHQ) were used to assess efficacy. In the double-blind, placebo controlled phase, a significant reduction in the Global Restless/Impulsive subscale of the CRS-P was observed; in addition, there was significant improvement in parent-impact emotional (PE) subscale of the CHQ (Manor et al., 2012). Additional analysis of a subgroup of children with more pronounced hyperactive and impulsive behavior demonstrated a significant reduction in ADHD-Index and hyperactive components (Manor et al., 2012). The open label extension showed sustained efficacy in the PS-Omega3 group; furthermore, children from the placebo group who switched to PS-Omega3 demonstrated a significant reduction in CRS-P and CRS-T subscale scores (Manor et al., 2012).

**Procyanidolic oligomers.** Procyanidolic oligomers (PCOs) derived from grape seed skin and maritime pine bark extract have been studied for their benefits in ADHD. One such study involved Pycnogenol, from maritime pine bark, in 61 children with ADHD. Fifty boys and 11 girls participated in a double-blind, placebo controlled trial in which they received 1 mg/kg Pycnogenol daily or placebo for four weeks (Trebatcika et al., 2006). At the beginning of the trial prior to intervention, after one month of treatment, and one month after termination of treatment, patients were evaluated by teachers and parents with the Child Attention Problems (CAP) teacher rating scale, Conner’s Teacher Rating Scale (CTRS) and Conner’s Parent Rating
Scale (CPRS) (Trebatcika et al., 2006). Fifty seven children completed the study. The results of the study showed a significant reduction in hyperactivity and improvements in attention and concentration in the Pycnogenol group compared to placebo (Trebatcika et al., 2006). One month after termination of Pycnogenol treatment, a relapse in ADHD symptoms was noted by the authors (Trebatcika et al., 2006).

**L-theanine.** Co-morbidities, including sleep disturbances, are common in ADHD. Lyon, Kapoor, and Juneja (2011). Examined the effects of l-theanine on sleep quality in boys with ADHD. Ninety eight boys, ages eight to 12 years, with ADHD participated in a randomized, double-blind, placebo controlled trial for 10 weeks. The patients were randomly assigned to take two 100 mg chewable tablets of l-theanine in the morning and two tablets after school or placebo (Lyon et al., 2011). Objective measures of sleep quality were assessed with actigraphy and subjective measures were assessed with the Pediatric Sleep Questionnaire (PSQ) (Lyon et al., 2011). The results showed that the l-theanine group experienced a significantly higher percentage of sleep efficiency and fewer bout of nocturnal activity, as demonstrated by actigraphy (Lyon et al., 2011). Although not statistically significant, the l-theanine group also experienced a lower number of minutes awake when compared to placebo (Lyon et al., 2011). L-theanine did not demonstrate benefit in time to fall asleep or sleep duration; as such, the authors concluded that l-theanine should be used only for sleep efficiency and nocturnal activity (Lyon et al., 2011).

**Botanicals.**

**Valerian and lemon balm.** A valerian and lemon balm leaf preparation were studied for its effectiveness in restlessness and dyssomnia, or nervous sleep disturbance in an open, multicenter study in children younger than 12. Nine hundred and eighteen children in total were
evaluated in this study (Muller and Klement, 2006). The participants were treated for at least four weeks and the dosage of the valerian/lemon balm preparation was determined by the investigator with a maximum of two tablets, two times daily (Muller and Klement, 2006). Each tablet contained 160 mg valerian root extract and 80 mg lemon balm leaf extract (Muller and Klement, 2006). The occurrence of symptoms was recorded at baseline and at the end of the study. At baseline, 61.7% reported daily occurrences of dyssomnia or restlessness; at the final visit, only 12.5% suffered from daily symptoms. The percentage of participants with severe restlessness changed from 28.1% at baseline to 4.5%; those with moderate levels decreased from 37.8% at baseline to 18.4% (Muller and Klement, 2006). Severe dyssomnia decreased from 33% to 3.6%, and moderate dyssomnia decreased from 35.6% to 18.5% (Muller and Klement, 2006). Additional subgroup analysis showed the valerian/lemon balm combination had benefit regardless of age (Muller and Klement, 2006). The authors concluded that the valerian/lemon balm combination could be a viable alternative to psychotropic medication with a high incidence of adverse effects (Muller and Klement, 2006).

A more recent study examined a valerian root/lemon balm combination in primary school children ages six to 11 years with hyperactivity, concentration difficulties, and impulsiveness (Gromball et al., 2014). This prospective, multi-center, open label study evaluated a total of 169 children who exhibited symptoms of ADHD, but did not meet the diagnostic criteria for ADHD as stated in the DSM-IV. Participants took two tablets twice daily of a fixed combination of valerian root extract and lemon balm extract for seven weeks. The daily dose of this fixed combination supplied 640 mg valerian root extract and 320 mg lemon balm extract (Gromball et al., 2014). Parents and physicians rated each child’s behavior at baseline, two weeks, and seven weeks. Symptoms included hyperactivity, impulsiveness, difficulties concentrating, difficulty
falling asleep and difficulty sleeping through the night (Gromball et al., 2014). At the end of the seven week treatment, physician ratings demonstrated a significant improvement in all of the aforementioned symptoms (Gromball et al., 2014). Fifty eight percent of parents rated their child’s behavior as a “heavy” or “very heavy” burden; this percentage decreased to 18% after the seven weeks (Gromball et al., 2014). The authors concluded that the valerian/lemon balm combination was safe and effective treatment for children ages six to 11 years with hyperactivity and difficulties with concentration but do not meet the diagnostic criteria for ADHD (Gromball et al., 2014).

Ginkgo biloba. A pilot study including 20 patients ages 6 to 13 years, tested a ginkgo leaf extract to determine the appropriate dosage and efficacy in treated ADHD symptoms. The participants were not using methylphenidate because of preference or tolerance issues (Uebel-von Sandersleben et al., 2014). Initially, participants used 40 mg twice daily for one week; the dosage was then increased to 60 mg twice daily and after another week to 120 mg twice daily (Uebel-von Sandersleben et al., 2014). The highest dose was taken for three more weeks. The primary outcome was a change in the component “severity of attentive problems” on the FBB-HKS questionnaire. Secondary outcomes included measurements of hyperactivity, impulsiveness, and aggression using the FBB-HKS and FBB-SSV. Significant changes were seen in attention and quality of life in participants using ginkgo (Uebel-von Sandersleben et al., 2014). The authors concluded that ginkgo was well-tolerated and could be useful as an alternative or adjuvant to standard treatment (Uebel-von Sandersleben et al., 2014).

Bacopa monnieri. An open label study of 31 children ages six to 12 years with ADHD was conducted to investigate the effectiveness of a standardized Bacopa monnieri extract in reducing the symptoms of ADHD. The children, diagnosed with ADHD according to the DSM-
IV criteria before the age of seven, received 225 mg of bacopa per day for six months (Dave et al., 2014). The outcome measure used was the Parent Rating Scale, which was administered at baseline and then at the end of the six month study (Dave et al., 2014). Symptom scores for restlessness were reduced in 93% of participants and self-control was improved in 89% of participants (Dave et al., 2014). Symptoms of attention-deficit were reduced in 85% of participants; reductions were also demonstrated for learning issues and impulsivity (Dave et al., 2014). Seventy four percent of children demonstrated a 20% reduction in total subtests scores and 26% of children showed between 21% and 50% reduction (Dave et al., 2014).

Kongkeaw et al. (2013) conducted a meta-analysis of randomized controlled trials on the cognitive effects of bacopa. Nine studies met the inclusion criteria and included 518 participants. The findings of the systematic review and meta-analysis showed that bacopa has the potential to improve cognition, especially speed of attention by reducing choice reaction time (Kongkeaw et al., 2013). Due to the improvement in attention, the authors suggested that bacopa could be an appropriate treatment for children with ADHD (Kongkeaw et al., 2013). The authors also identified a trial of 100 mg bacopa extract daily for 12 weeks increased cognitive performance in children with ADHD (Kongkeaw et al., 2013).

**Anxiety and Depression**

**Dietary interventions.** According to Gaby (2011), reactive hypoglycemia is a common contributing factor in anxiety. To counteract the compensation of the sympathetic nervous system’s response to falling blood glucose levels, Gaby (2011) recommends the avoidance of refined sugar and refined carbohydrates; in addition, six small meals should be consumed per day. These meals should consist of high protein and high complex carbohydrates (Gaby, 2011).
Caffeine consumption can also impact the development of the symptoms of anxiety. Excessive caffeine intake can cause symptoms that are indistinguishable from those of anxiety. Early studies on caffeine intake and anxiety show that anxiety patients may be more sensitive to the anxiety-inducing effects of caffeine. In one of these early studies, 83 psychiatric in-patients were evaluated for their caffeine intake. Twenty-two percent of these patients reported a habitual intake of caffeine equaling 750 mg per day or more (Procter and Greden, 1982). These particular patients experienced significantly more severe anxiety than patients who consumed less caffeine (Procter and Greden, 1982). In another study on 14 psychiatric in-patients, a restriction of caffeine intake for three weeks resulted in significant improvements in scales used to measure anxiety (DeFreitas and Schwartz, 1979). Furthermore, these improvements reversed when caffeine was reintroduced (DeFreitas and Schwartz, 1979).

**Supplemental nutrients.**

**Magnesium.** Magnesium deficiency can cause anxiety and a decreased tolerance to stress. Physiologically, magnesium acts as an N-methyl-D-aspartate (NMDA) glutamate receptor inhibitor (Poleszak, et al., 2004). The antidepressant and anxiolytic activity of magnesium was studied in mice using forced swim test and elevated maze test. Poleszak et al. (2004) demonstrated that at 20 mg and 30 mg per kg, magnesium exerted antidepressant activity by reducing immobility time in the swim test; in addition, the same doses produced an anxiolytic effect in the maze test.

Dietary intake of magnesium has also been associated with depressive symptoms. Yary, Aazami and Soleimannejad (2012) conducted a cross-sectional study of 425 post-graduate students to assess the relationship between magnesium intake and depressive symptoms. Four hundred and two samples which included 173 women and 229 men were included and analyzed.
A self-administered questionnaire, the CES-D was used to measure depressive symptoms and dietary magnesium intake was assessed using a food frequency questionnaire (FFQ). One hundred twenty two participants had clinically relevant depressive symptoms. The results of the study demonstrated an inverse relationship between magnesium and depressive symptoms (Yary et al., 2012). This relationship persisted even after adjustments for sex, age, BMI and other factors (Yary et al., 2012).

Miki et al. (2014) examined data from the Furukawa Nutrition and Health Study, which included 2162 survey participants, to determine the associations between the intake of minerals, including magnesium and the prevalence of depressive symptoms among Japanese employees. Dietary intake of minerals was assessed using a validated self-administered diet history questionnaire which consisted of the following five sections: intake frequency of 46 food and nonalcoholic beverages; daily intake of rice and miso soup; frequency of alcoholic consumption and the amount of consumption for five alcoholic beverages per typical occasion; usual cooking methods and general dietary behavior (Miki et al., 2012). The intake of selected nutrients, including magnesium, was estimated via algorithm (Miki et al., 2012). Depressive symptoms were assessed using the Japanese version of the CES-D Scale. The results showed that depressive symptoms tended to decrease with an increasing level of minerals. Statistically significant trend associations were observed specifically for magnesium (Miki et al., 2012).

Cheungpasitporn et al. (2015) conducted a systematic review and meta-analysis to assess the association between hypomagnesaemia and depression. Six observational studies (three cohort studies, two cross-sectional studies and one case-control study) with a total of 19,137 participants were included in the meta-analysis. The results of the data analysis demonstrated a potential association between depression and hypomagnesaemia (Cheungpasitporn et al., 2015).
The authors’ findings showed an overall 1.34-fold increased risk of hypomagnesaemia compared with those participants who did not have hypomagnesaemia (Cheungpasitporn et al., 2015). The authors concluded that their meta-analysis could demonstrate only an association, but not a causal relationship due to the observational nature of the studies included (Cheungpasitporn et al., 2015).

**Folate and Vitamin B<sub>12</sub>.** Depression is a symptom of both vitamin B<sub>12</sub> and folate deficiency. Several studies have examined the relationship between folate and vitamin B<sub>12</sub> and depression. Coppen and Bailey (2000) investigated folic acid as an adjuvant to enhance the antidepressant action of fluoxetine. One hundred and twenty seven patients were randomly assigned to receive either 500 µg of folic acid or a placebo in addition to 20 mg fluoxetine daily for 10 weeks. Patients met the DSM-III-R criteria for major depression and at baseline had Hamilton Rating Scale score for depression of 20 or more. The fluoxetine plus folic acid group demonstrated a significantly greater improvement in the mean Hamilton Rating Scale, which was 6.8 at completion of the study, compared to 11.7 in the fluoxetine plus placebo group (Coppen and Bailey, 2000). Interestingly, this finding was observed only the women (Coppen and Bailey, 2000). The authors concluded that folic acid greatly improves the antidepressant action of fluoxetine and likely other antidepressants; in addition, men require higher levels than women (Coppen and Bailey, 2000).

Papakostas et al. (2012) conducted two multicenter sequential parallel comparison trials to examine the effect of adjunctive L-methylfolate in the treatment of major depressive disorder in patients with partial response or no response to selective serotonin reuptake inhibitors (SSRIs). In the first trial, participants were randomized to one of three treatment groups; the study was divided into two 30-day phases. One group received two placebo pills during phases I and II
(Papakostas et al., 2012). The second group received two placebo pills during phase I and one placebo and one 7.5 mg L-methylfolate pill during phase II (Papakostas et al., 2012). The third group received one placebo and one 7.5 mg L-methylfolate in phase I and two 7.5 mg L-methylfolate pills in phase II (Papakostas et al., 2012). SSRI dosages remained constant during phase I and phase II (Papakostas et al., 2012). One hundred and nineteen patients completed the study. The results of the first trial showed that 7.5 mg per day of adjunctive L-methylfolate was not efficacious; however, the group who used an increased dosage of 15 mg per day had a greater response rate than those on SSRI plus placebo, with 24% compared to 9% (Papakostas et al., 2012). Based on the results of the first trial, the second trial used only 15 mg per day of L-methylfolate. The results of the second trial demonstrated that adjunctive L-methylfolate was superior to SSRI plus placebo with statistical significance in both response rates and degree of improvement on the HAM-D (Papakostas et al., 2012).

Based upon the hypothesis that sufficient amounts of vitamin B₁₂ and folate are necessary for the function of neurological pathways for mood regulation, Penninx et al. (2000) used data from the Women’s Health and Aging Study to examine whether older women living in community with vitamin B₁₂ or folate deficiency were more likely to suffer from depression. Serum levels of vitamin B₁₂, folate, methylmalonic acid and total homocysteine were assayed in 700 disabled, nondemented women aged 65 years or older. High levels of serum methylmalonic acid and homocysteine combined with low serum vitamin B₁₂ and folate were used by the authors to better determine vitamin deficiency in tissue (Penninx et al., 2000). Depressive symptoms were measure by the Geriatric Depression Scale, which has scores that range from zero to 30, with higher scores signifying high levels of depressive symptoms. Results of this study showed that of the 700 participants, 68.3% were not depressed, 14.3% were mildly
depressed and 17.4% were severely depressed (Penninx et al., 2000). Vitamin B\textsubscript{12} deficiency occurred in 17.3% of the participants and folate deficiency was found in 7.1% of participants (Penninx et al., 2000). Only 2.6% of the participants had both folate and vitamin B\textsubscript{12} deficiency (Penninx et al., 2000). Vitamin B\textsubscript{12} deficiency was found significantly more often in women considered severely depressed and mildly depressed when compared to nondepressed women (Penninx et al., 2000). The authors stated that women with a metabolically significant vitamin B\textsubscript{12} deficiency had more than twice the risk of depression than women without such a deficiency (Penninx et al., 2000).

Syed, Wasay and Awan (2013) conducted a randomized controlled trial investigating antidepressant monotherapy compared to adjuvant vitamin B\textsubscript{12} therapy in a population sample of depressed Pakistani patients with low normal B\textsubscript{12} levels. Seventy three patients with low normal Vitamin B\textsubscript{12} levels participated in this study, with 34 randomized to the treatment group and 39 randomized to the control group. The control group received only antidepressants, while the treatment group received antidepressants plus a 1,000 µg B\textsubscript{12} intramuscular injection every week (Syed et al., 2013). Depression was defined using the HAM-D rating scale with a score of $\geq 16$. The primary outcome was defined as a decline in the HAM-D score of 20% or more from baseline (Syed et al., 2013). The results demonstrated that at three month follow up, 100% of the treatment group showed at least a 20% reduction in HAM-D score, compared to 69% in the control arm. The authors noted that due to financial constraints they were not able to obtain the final serum levels of vitamin B\textsubscript{12} in the participants; however, they concluded that in their sample group, vitamin B\textsubscript{12} supplementation with antidepressants significantly improved depressive symptoms (Syed et al., 2013).
**Omega-3 fatty acids.** Osher and Belmaker (2009) reviewed three studies of omega-3 fatty acid supplementation for the treatment of depression that were conducted at the Beer Sheva Mental Health Center in Israel. The first study involved patients with recurring unipolar depression on maintenance antidepressant therapy. The study was designed as a four week parallel group, double-blind add on (Osher and Belmaker, 2009). A total of 20 patients with at least three weeks of ongoing antidepressant drug therapy and a score of at least 18 on the HAM-D participated in the study (Osher and Belmaker, 2009). The treatment group received 1 gram, twice daily of EPA ethyl ester for four weeks. EPA was significantly different from placebo beginning at week two and through the end of the study (Osher and Belmaker, 2009). The mean reduction of the HAM-D was 12.4 points in the EPA group, compared to placebo (Osher and Belmaker, 2009). Six out of 10 patients in the EPA group demonstrated a 50% reduction in HAM-D, while only one of 10 patients in the placebo group achieved that reduction (Osher and Belmaker, 2009). The second trial, a controlled study, investigated omega-3 fatty acids in childhood depression specifically in children under age 12 (Osher and Belmaker, 2009). The 16-week trial used the Childhood Depression Rating Scale (CDRS), Childhood Depression Inventory (CDI) and Clinical Global Impression (CGI) scales at baseline, two weeks, four weeks, eight weeks, 12 weeks and 16 weeks (Osher and Belmaker, 2009). Twenty eight children participated in the trial and were randomized to receive either two 500 mg or one 1,000 mg capsule of omega-3 fatty acids or two 500 mg placebo capsules or one 1,000 mg placebo capsule (Osher and Belmaker, 2009). The 1,000 mg omega-3 capsule contained 400 mg EPA and 200 mg DHA and the 500 mg active capsules contained 190 mg EPA and 90 mg DHA (Osher and Belmaker, 2009). The placebo consisted of 500 mg olive oil or 1,000 mg safflower oil (Osher and Belmaker, 2009). Twenty children completed the trial. Of the children in the omega-3
group, seven out of 10 had a greater than 50% reduction in CDRS; no patients in the placebo group experienced a greater than 50% reduction (Osher and Belmaker, 2009). At the end of the study, four out of 10 children in the omega-3 group met the remission criteria of CDRS (Osher and Belmaker, 2009). The third study reviewed was an open label trial of EPA in bipolar depression involving 12 bipolar patients. Two patients experienced resistant depression; two experienced breakthrough depression while on mood stabilizing drugs; one patient experienced breakthrough depression while on mood stabilizers and antidepressants; four patients had residual depressive symptoms while on lithium; four patients experienced an onset of depression with three of these patients using omega-3s as a monotherapy (Osher and Belmaker, 2009). HAM-D 24 Rating Scales were used at baseline and monthly for up to six months (Osher and Belmaker, 2009). Patients received 2 g of EPA daily (Osher and Belmaker, 2009). At the end of this study, results showed that eight of 10 patients had a 50% or greater reduction in HAM-D scores within one month (Osher and Belmaker, 2009). The authors noted that the results of the bipolar study were preliminary and the encouraging results were justification for larger trials (Osher and Belmaker, 2009). Taken as a whole, the authors concluded that omega-3 fatty acids were demonstrated to be more effective than placebo for depression in both children and adults; furthermore, these results warranted continued research (Osher and Belmaker, 2009).

Ginty and Conklin (2015) conducted a study to examine the effects of acute and low dose long-chain omega-3 polyunsaturated fatty acids (LCPUFAs) supplementation in young adults with depression. Twenty three participants were randomized to receive 1.4 g of LCPUFAs consisting of 1 g EPA and 400 mg DHA or placebo (corn oil) for 21 days (Ginty and Conkin, 2015). All participants had a score of 10 or above on the Beck Depression Inventory (BDI), which was completed at visit one and visit 2, 21 days after supplementation. Twenty one
participants completed the study. The results showed that 67% of the LCPUFA group had a BDI score lower than 10, while only 20% of the placebo group met these criteria (Ginty and Conklin, 2015). This result was significant at p = 0.04 (Ginty and Conklin, 2015). The authors concluded that LCPUFAs, equivalent to adding two fatty fish meals per week, reduced depressive symptoms and depression below clinical levels (Ginty and Conklin, 2015).

**Botanicals.**

**St. John's Wort.** A randomized, double-blind, placebo-controlled trial was conducted with 21 primary care physicians in Germany and included 388 men and women from 18 to 70 years old who were suffering from moderate depression (Gastpar, Singer and Zeller, 2006). Participants were randomized to receive one of three possible treatments: 900 mg of STW3-VI, a St. John’s wort extract, once daily; 20 mg citalopram once daily; and placebo once daily (Gastpar, Singer and Zeller, 2006). Participants took the treatments in the morning for six weeks. Participants were evaluated at baseline, and on days seven, 21 and 42 using HAM-D 1-17, the von Zerssen’s Adjective mood Scale and CGI scales (Gastpar, Singer and Zeller, 2006). Three hundred sixty eight patients completed the study. In the STW3-VI group, HAM-D score improved from baseline to day 42, from 21.9 to 10.3, in the citalopram group from 21.8 to 10.3 and in the placebo group from 22.0 to 13.0 (Gastpar, Singer and Zeller, 2006). The results indicated that STW3-VI was therapeutically equivalent to citalopram and superior to placebo (Gastpar, Singer and Zeller, 2006). Fewer participants in the STW3-VI group experienced adverse events at 29.8%, compared to 41.7% in the citalopram group (Gastpar, Singer and Zeller, 2006). The authors concluded that St. John’s wort extract, STW3-VI, was a good alternative to antidepressant drugs for patients with moderate depression; in addition, the St. John’s wort
extract demonstrated better tolerability and safety when compared to citalopram (Gastpar, Singer and Zeller, 2006).

Linde, Berner and Kriston (2008) updated the Cochrane Review on St. John’s wort (SJW) to investigate whether SJW extracts are more effective than placebo and as effective as standard antidepressant treatment for major depression; in addition, the occurrence of adverse events is also examined. A total of 79 studies were identified and of those, 29 studies with 5,489 patients met the inclusion criteria. Eighteen were placebo-controlled and 17 were active-controlled studies (Linde et al., 2008). Depression was rated as mild to moderate in 19 trials and moderate to severe in nine trials; one trial did not specify the severity (Linde et al., 2008).

Several different SJW products were used in the trials and ranged in daily dose from 240 mg to 1,800 mg. Most studies used a daily dose between 200 mg and 500 mg (Linde et al., 2008). The active controls included fluoxetine, sertraline, imipramine, citalopram, paroxetine, maprotiline, and amitriptyline. Duration of the trials ranged from four weeks to 12 weeks. In reviewing the placebo-controlled trials, participants who received SJW were significantly more likely to be responders (Linde et al., 2008). Remission rates were also significantly higher in the SJW groups when compared to placebo (Linde et al., 2008). In the active comparison trials that compared SJW to standard antidepressant drug treatments, data analysis based on the HAM-D demonstrated to statistical differences between the groups; CGI also found no differences (Linde et al., 2008). The two treatment groups were essentially the same. Patients reporting adverse events were more frequent in the antidepressant drug treatment groups; hence, patients receiving SJW were less likely to drop out of a study due to adverse effects (Linde et al., 2008). The authors concluded that their overall findings support the use of SJW for the treatment of major depression; furthermore, SJW appeared to safe and effective (Linde et al., 2008).
**Rhodiola rosea.** Darbinyan et al. (2007) conducted the first known randomized, double-blind, placebo-controlled trial examined the effects of a *Rhodiola rosea* extract, SHR-5 for the treatment of mild to moderate depression. At total of 89 participants, male and females ages 18 to 70 years were included in the study. All participants were selected according to DSM-IV diagnostic criteria for depression; the severity of depression was determined with the BDI and HAMD questionnaires (Darbinyan et al., 2007). Patients with HAMD scores between 21 and 31 were randomly assigned into three groups: group A received two tablets daily of SHR-5 at 340 mg per day; group B received two tablets twice daily of SHR-5 at 680 mg per day and group C received two placebo tablets daily (Darbinyan et al., 2007). Prior to the start of the trial, all participants underwent a 2-week run-in period in which they received no medication. Treatment began after this two week period. BDI and HAMD questionnaires were given to participants at the start and the end of trial, on day 42 (Darbinyan et al., 2007). The results showed a statistical difference in the mean HAMD and BDI scores after 42 days of treatment with SHR-5 (Darbinyan et al., 2007). The mean total HAMD scores decreased from 24.52 at baseline to 15.97 in group A and from 23.79 to 16.72 in group B (Darbinyan et al., 2007). The placebo group C showed no improvement in HAMD scores. Treatment groups A and B also experienced significant improvements in four HAMD subgroups: insomnia, emotional instability, somatization and self-esteem (Darbinyan et al., 2007). The authors concluded that rhodiola possesses antidepressant activity in patients with mild to moderate depression; furthermore there were no side effects in either SHR-5 treatment group (Darbinyan et al., 2007).

**Withania somnifera (Ashwagandha).** Andrade et al. (2004) performed a double-blind, placebo-controlled trial to evaluate the efficacy of an extract of Ashwagandha in patients with ICD-10 anxiety disorders. Thirty nine patients were randomized to receive either 250 mg of
ashwagandha extract or placebo, taken as two tablets twice daily, with a minimum of two tablets daily and a maximum of 10 tablets daily depending upon clinical response and adverse events reported (Andrade et al., 2004). Patients were assessed at baseline, week two and week six using the Hamilton Anxiety Scale, Global Rating Scale and Systematic assessment for treatment emergent effects (SAFTEE) symptom checklist (Andrade et al., 2004). At total of 12 patients dropped out of the study for various reasons. The results demonstrated a trend for anxiolytic superiority of ashwagandha over placebo at week two, although these results were not statistically significant (Andrade et al., 2004). Statistically significant superiority over placebo was demonstrated at week six of the study, with 15 of 17 participants in the ashwagandha group meeting criteria for response (Andrade et al., 2004).

A prospective, randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of a high-concentration extract of Ashwagandha in reducing stress and anxiety in adults under stress. At total of 64 participants with a history of chronic stress were included in the study for duration of 60 days (Chandrasekhar, Kapoor and Anishetty, 2012). On day zero, serum A.M. cortisol levels were measured. The participants were administered three questionnaires: Perceived Stress Scale (PSS), Depression Anxiety Stress Scale (DASS) and the 28-item version of the General Health Questionnaire (GHQ-28) (Chandrasekhar et al., 2012). Each subject was randomly assigned to either the treatment group or the placebo control group. The treatment group received 300 mg capsules of high-concentration, full-spectrum Ashwagandha root extract and were instructed to take once capsule twice daily for 60 days (Chandrasekhar et al., 2012). Sixty one participants completed the study. The results demonstrated a 44% reduction in baseline PSS scores in the Ashwagandha group compared to 5.5% in the placebo group (Chandrasekhar et al., 2012). In the GHQ-28 scale, the ashwagandha
group experienced reductions for the following item subsets: somatic, 76.1%; anxiety and insomnia, 69.7%; social dysfunction, 68.1%; severe depression, 79.2% (Chandrasekhar et al., 2012). These reductions were significantly higher when compared to placebo. On the DASS scale, the Ashwagandha group experienced significant reduction in the following item subsets: depression, 77%; anxiety, 75.6%; stress, 64.2% (Chandrasekhar et al., 2012). Compared to placebo, these reductions were significantly higher.

**Discussion**

**Pain Management**

The accepted definition of pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage” (Berry et al., n.d.) It is well understood that pain is wholly subjective to the individual experiencing it. As defined, pain is a complex response that involves both the physical and the emotional. CAM therapies for pain management have the distinct ability to reach the emotional facets of pain management whereas conventional drug therapies do not possess such abilities. The results of this literature review demonstrate the benefits of mind-body therapies, such as yoga and meditation for pain management. With these types of CAM therapies, the benefits cannot always be pinpointed in the scientific realm. Some of the benefits of yoga, for instance, may be rooted in its psychosocial effects by reducing social isolation, as it is often practiced in groups; furthermore, the psychological changes produced by the practice of yoga can increase an individual’s awareness of his or her mental and physical state (Wren, et al., 2011). This increased awareness provides the individual with a better understanding of his or her pain. The same effect can be said for mindfulness meditation, which can be used to shape the very perception of a person’s sensory environment. The benefits of both yoga and meditation may also be linked to stress reduction,
which can lead to better pain management. It is now recognized that several clinical pain conditions are influenced by a person’s levels of stress and are associated with changes in the HPA axis. Strong evidence also exists for the ancient practice of acupuncture to alleviate and manage many pain conditions, such as migraine and chronic pain. The CAM therapies presented in the literature review for pain management offer people suffering with chronic pain a viable alternative to the conventional pathway for pain management. This conventional pathway usually ends in the use of powerful and highly addictive opioid pain medication. The botanical therapies presented in this literature review have none of the serious adverse events associated with opioid pain medication. While botanicals alone may not reach the power of morphine-derivative drugs, combinations of acupuncture, stress management and herbal therapies can offer people meaningful and lasting results that reach well beyond the superficial effects of pain medication. Given that 25.3 million Americans struggle with daily pain, the need for alternative means of treatment will continue (NCCIH, 2015).

**ADHD**

As of 2011, 6.4 million children had been diagnosed with ADHD (CDC, 2015). More and more families are looking toward CAM therapies to decrease the symptoms of ADHD and improve their children’s quality of life. The adverse events associated with ADHD medications and potential safety issues surround the long-term use of these drugs makes an integrative approach to this complex disease all the more relevant. The results of the literature review on ADHD demonstrate that dietary interventions and supplementation with nutrients and botanicals can decrease the symptoms of ADHD. Furthermore, many of these CAM options can be combined with current ADHD drug therapies. While dietary interventions can be time consuming, simple changes such as choosing organically grown foods over conventional foods
can have an impact by reducing exposures to known environmental toxins associated with ADHD risk. CAM therapies for ADHD can be a great benefit for those children who are nonresponders to conventional drug treatments. For these children, REDs, fish oil and botanicals may be their only option for the management of ADHD symptoms.

**Anxiety and Depression**

Evidence continues to emerge that links anxiety and depression to several nutrient-based issues. Deficiencies in magnesium, B_{12}, folate and omega-3 fatty acids have all been associated with a higher risk of developing anxiety and depression. The results presented in this literature review support the idea that dietary changes paired with supplementation of specific nutrients can potentially influence the symptoms of both anxiety and depression. Nutrients including folate and vitamin B_{12} can be safely combined with antidepressant therapies, particularly for those individuals suffering from depression that is resistant to current drug treatments. Considering the majority of Americans do not consume the recommended 400 mg of magnesium daily, the role of magnesium deficiencies deserve more attention in depression and anxiety. Herbal interventions, especially St. John’s wort, not only have the evidence to prove efficacy in depression, but also the evidence to show that they are associated with a very low incidence of adverse events. Compliance with current antidepressants drug treatments is problematic for patients with depression and herbal products offer viable options for people who experience serious adverse events with drug therapy.

**Conclusions and Recommendations**

CAM therapies are useful tools and viable options for individuals struggling with pain, ADHD and anxiety and depression. While some interventions require more robust clinical studies, the majority of CAM interventions for pain management, ADHD and anxiety and
depression have the evidence to prove efficacy and safety. The evidence presented in this literature review support the use of CAM therapies as adjuvants and/or monotherapies for the aforementioned conditions.

For individuals and families struggling with pain, ADHD, anxiety or depression, mind-body therapies including yoga and meditation are CAM therapies that can provide significant results for stress management. As chronic stress contributes negatively to all of these conditions, learning ways to manage stress is crucial to creating balancing and improving health. Yoga is readily accessible in many communities across the country and should be seriously considered, even for children.

As it relates to anxiety and depression specifically, some people may be weary of using St. John’s wort after the very negative publicity regarding drug interactions; however, there are other nutrients that can be easily combined with current antidepressant therapies. Evidence on these nutrients: folate, vitamin B₁₂, magnesium and omega-3 fatty acids have been presented here in this paper.

Modern medicine is at a place where it needs to move toward integrative practices, incorporating CAM therapies. We are past the time of brushing them off as quackery. Many of them have proven efficacy with very limited side effects. In a country where 80% of the world’s prescriptions for opioid pain killers are written, where 6 million children have been diagnosed with ADHD and where depression is predicted to be the second leading cause of disability in the next four years, it is time to change course.
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