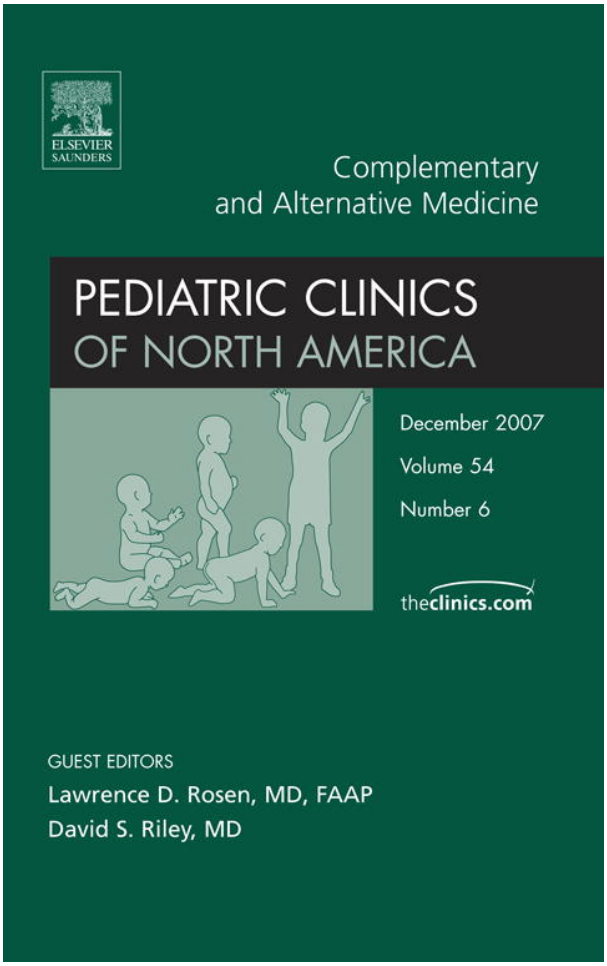

ELSEVIER
SAUNDERS

PEDIATRIC CLINICS
OF NORTH AMERICA

Pediatr Clin N Am 54 (2007) 901–926

Complementary and Alternative Medicine Therapies to Promote Healthy Moods

Kathi J. Kemper, MD, MPH[a,*], Scott Shannon, MD[b]

[a]*Pediatrics and Public Health Sciences, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA*
[b]*Northern Colorado Center for Holistic Medicine, 7603 Colland Drive, Fort Collins, CO 80525, USA*

Pediatric mood disorders (unipolar depression and bipolar disorder) are serious, common, persistent, and recurrent medical conditions. The US National Institute of Mental Health and the World Health Organization estimate that depression is the leading cause of disability in the United States, and worldwide, it is the second-leading contributor to the global burden of disease for persons 15 to 44 years old [1].

Mood disorders have several nonmodifiable risk factors, including family history, gender, and race. Major depression and suicide are associated with fewer serotonin transporter sites in the prefrontal cortex of the brain. Lower norepinephrine levels are associated with dysphoria and apathy. Central nervous system dopamine levels are also reduced in depression. Before puberty, the prevalence of depression is higher in boys than in girls; after puberty, the rates in girls are about twice those in boys. Native Americans have higher rates of depression, whereas Asians report fewer depressive symptoms than Caucasians.

Mood disorders have a high rate of comorbidity with mental health and medical problems. For example, many children and adolescents suffering from attention-deficit/hyperactivity disorder, anxiety, or substance abuse also suffer from depression, and vice versa. Depressive disorders are also common among patients who have chronic medical conditions, including

Dr. Kemper is supported in part by the Kohlberg Foundation, by NIH NCCAM K24 AT002207 and NIH NCAM R21 AT001901, and by the Caryl Guth Fund for Holistic and Integrative Medicine. The views expressed in this article are those of the authors and do not necessarily represent the views of the Kohlberg Foundation, the NIH, or Dr. Guth.

* Corresponding author.
E-mail address: kkemper@wfubmc.edu (K.J. Kemper).

doi:10.1016/j.pcl.2007.09.002

any condition causing chronic pain, obesity, endocrine disorders, inflammatory disorders, cancer, anemia, viral infections, and brain injury. Depression can also be caused by medications, including antihypertensive medications and oral contraceptives. Depression recurs in 70% of those affected. Therefore, even patients who have improved should actively pursue activities to promote positive moods and prevent recurrences.

Mainstream therapies, such as medications, cognitive behavioral therapies, electroconvulsive therapy, and vagal nerve stimulators have been discussed extensively in other reviews [2–5]. Furthermore, given the side effects and stigmatization of standard antidepressant medications, many families turn to complementary therapies. In fact, depression is one of the most common reasons for adolescents and adults to seek complementary therapies [6].

Therefore, the focus of this article is the fundamental lifestyle approaches and complementary therapies that enhance mental health, particularly those that help achieve and maintain healthy moods. The emerging term to describe the use of lifestyle and complementary therapies in combination with traditional, scientific medicine is ''integrative medicine.'' Integrative medicine is informed by science and is based on four core concepts:

- Patient-centered care (individualized, consistent with patient values and goals)
- Sustainable, healing environment
- Comprehensive approach to therapies
- Health promotion and wellness; promotion of the innate healing potential

Health: physical and mental

Mental health is closely tied to physical health. A successful athlete exhibits strength, flexibility, endurance, coordination, focus, resilience, teamwork, and sport-specific skills. Similarly, a mentally healthy person exhibits confidence, courage, cheerfulness, coping abilities, hardiness, and focused attention. It's not that the fit athlete never stumbles or that he/she always hits a home run, but that, barring a catastrophe, he/she can get up and try again. Similarly, a mentally healthy person occasionally experiences sadness, worry, misery, exhilaration, ecstasy, and the full range of human emotions, recognizing that ''into each life, some rain must fall,'' but views the rain as a challenge rather than an insurmountable obstacle. Holistic physicians also consider spiritual health as a critical element of overall health. Table 1 shows some of the characteristics of physical, mental, and spiritual health.

Because the mind–body connection is real, promotion of mental health, including healthy moods, relies on very similar strategies to those promoting physical health.

Table 1
Physical, mental, and spiritual health characteristics

Physical fitness	Mental health	Spiritual health
Strength	Confidence and courage	Faith
Flexibility	Adaptability	Forgiveness
Endurance	Cheerfulness	Hope
Focus	Focus and attention	Love
Coordination	Harmony	Kindness
Resilience	Hardiness	Charity and generosity
Teamwork	Social network, communication skills, and connection to community	Connection with a higher power

Therapeutic options for achieving healthy moods fall into four major categories:

- Lifestyle
- Biochemical
- Biomechanical
- Bioenergetic

Lifestyle essentials: the fundamentals for healthy moods

Successful athletic coaches emphasize the fundamental skills of their sport. When it comes to mental and physical health, the fundamentals are excellent nutrition (including avoiding toxic ingestions and inhalations while optimizing the intake of essential nutrients); exercise balanced with restful sleep; a healthy environment (such as plenty of sunshine; mood-boosting music; minimal environmental and psychosocial toxins; and supportive family, friends, and community); and mind–body therapies and techniques (such as meditation and relaxation) [7]. In a German study, intensive lifestyle therapy was as effective as counseling and medication in improving depressive symptoms [8].

Nutrition

Healthy nutrition means taking in optimal amounts of essential nutrients while avoiding or minimizing the intake of toxic substances. Individual genetic variability, previous dietary patterns, medical illnesses, medications, allergies, and environmental exposures may increase the need for specific nutrients in the form of supplements.

Evidence-based guidance includes the following suggestions:

- Promote stable blood sugar by encouraging foods with a low glycemic index, such as proteins and complex carbohydrates [9].
- Encourage patients to eat breakfast, including some protein, to promote stable blood sugar throughout the day [10–12].
- Minimize the use of processed foods.

- Emphasize drinking plenty of pure water and eating fresh fruits and vegetables, legumes, whole grains, fish, and, if dairy and meat are eaten, organic, locally raised products whenever possible.
- Avoid sweetened beverages, processed foods, fatty foods, fried foods, and junk food.

Approximately 6% to 10% of children have allergies or sensitivities to foods, including 1% who cannot tolerate gluten [13]. The most common food sensitivities are to wheat, corn, soy, dairy, eggs, tree nuts, shell fish, and peanuts. Food sensitivities can cause mood problems in addition to rashes, asthma, and rhinorrhea [14,15]. Detection of food sensitivities begins with keeping a careful food diary. In some cases, blood testing, skin testing, endoscopic biopsy (for gluten sensitivity), and elimination diets may be useful in diagnosing food sensitivities. Eliminating the triggering food or foods from the diet can improve mood [14,15] and other symptoms such as chronic headaches, rashes, and gastrointestinal upset. Children with multiple food sensitivities may benefit from nutritional counseling to ensure adequate intakes of essential nutrients [16].

One should avoid toxic ingestions. Some people try to manage their moods by smoking, drinking alcohol, or taking other drugs. Although these may improve mood in the short term, over the longer term, they contribute to many miseries. Rarely, people are sensitive to petrochemicals, artificial flavors, artificial colors, and artificial sweeteners; these food additives are not essential nutrients and can easily be avoided by most people. Choosing organic food is a good way to ensure freedom from chemical residues. Pediatricians can advocate for farm, nutrition, and environmental policies that are health promoting.

One should ensure an adequate intake of the nutrients essential to healthy mood. Nutrients are essential for optimal production of neurotransmitters affecting mood, such as serotonin (made from tryptophan, with B vitamins and zinc as cofactors). The easiest way for most bodies to absorb nutrients is through unprocessed, locally grown, organic foods. Table 2 provides a listing of food sources for nutrients essential for mental health.

Exercise and rest

For many people, vigorous physical exercise is as effective as, or more effective than, antidepressant medications in promoting positive moods. Children who are sedentary report higher levels of depression [12,17,18]. Depressed mood and fatigue are common in individuals deprived of the usual exercise activities (whether from an injury or acute illness), and may be partially mediated by reduced fitness levels [19]. Getting kids away from the television, computer, and electronic games in favor of vigorous activity can improve mood. In a meta-analysis of yoga therapy, five randomized controlled trials (RCTs) in adults suffering from depression all reported positive effects of exercise [20]. No adverse effects were reported, with the

Table 2
Nutrients essential for mental health and their food sources

Nutrient	Food sources
Essential fatty acids (omega-3 fatty acids such as linolenic acid)	Fish (tuna, salmon, and mackerel) fish oil, flax seeds, flax oil, canola oil, walnut oil, dark green leafy vegetables
Vitamin B_6	Beans, nuts, legumes
	Eggs, meats, fish
	Whole grains and fortified breads and cereals
Vitamin C	(All fruits and vegetables contain some amount of vitamin C.) Green and red peppers, citrus fruits and juices, strawberries, tomatoes, broccoli, turnip greens and other leafy greens, sweet and white potatoes, cantaloupe, papaya, mango, watermelon, Brussels sprouts, cauliflower, cabbage, winter squash, raspberries, blueberries, cranberries, and pineapples
Folate	Beans and legumes
	Citrus fruits and juices
	Wheat bran and other whole grains
	Dark green leafy vegetables
	Poultry, pork, shellfish
	Liver
Calcium	Milk, yogurt, buttermilk, cheese
	Calcium-fortified orange juice
	Green leafy vegetables (broccoli, collards, kale, mustard greens, turnip greens, and bok choy or Chinese cabbage)
	Canned salmon and sardines canned with their soft bones
	Shellfish
	Almonds, Brazil nuts
	Dried beans
Vitamin D	Fish, fish oils, oysters
	Fortified foods such as cow milk, soy milk, and rice milk, and some cereals
Tryptophan	Turkey, chicken, fish
	Milk, cheese
	Eggs
	Soy, tofu
	Sesame seeds
	Pumpkin seeds
	Tree nuts, peanuts, peanut butter
Zinc	Beef, pork, lamb, oysters, dark meat of poultry
	Peanuts, peanut butter, nuts, and legumes (beans)
	Fortified cereals

exception of fatigue and breathlessness in participants in one study. The side effects of exercise include over-use injuries, decreased obesity, lower risk of heart disease, improved sleep, less chronic fatigue, improved academic performance, and decreased pain. Clinicians should advise patients suffering from depression to maintain a healthy lifestyle by exercising regularly.

Sleep deprivation can lead to poor mood, and insomnia is a common symptom of depression [21]. Many teenagers do not get sufficient sleep. Improving sleep hygiene (using the bed only for sleep, removing the television from the

bedroom, ensuring that the bedroom is dark and cool, taking a hot bath before bed, listening to relaxing music, reading positive or inspiring books, receiving a brief massage from a trusted family member, and writing in a journal before bed) can help improve mood and set the tone for a restful sleep.

Environment

A healthy environment is of critical importance in promoting, maintaining, and restoring healthy mood. An environment that includes poverty, abuse, neglect, or absence of opportunities for work or school can have severe adverse effects on mood that cannot be corrected through medications alone. The key elements that affect mood in the physical environment (eg, light, nature), the psychologic environment (eg, television), the social and cultural environment (racism, sexism, poverty, and social isolation) are touched on here.

Songs, poems, stories, and folk wisdom support the association between sunshine and happiness, and lack of sunshine and sadness (the blues). Bright light suppresses daytime melatonin production and shifts circadian rhythms. Desynchronization of internal rhythms plays an important role in the pathophysiology of depressive disorders. Serotonin levels are lowest during the winter months. Seasonal affective disorder has been well described. Given the modern lifestyles of living indoors and traveling in enclosed vehicles, modern children and adolescents receive far less sunshine than our ancestors. Psychiatrists have noted that depressed patients hospitalized in sunny rooms have shorter lengths of stay than patients in less sunny rooms [22].

Sunlight is an essential component of our natural environment. Daylighting, the practice of enhancing direct daylight exposure for children in classrooms, enhances school performance, reduces illness, and improves attendance [23]. Bright light therapy plays an effective role in the treatment of mood disorders. In an RCT published in 2006, bright light was as effective as fluoxetine in improving symptoms of seasonal affective disorder (67% response rate for both) [24]. Phototherapy has also been as effective as antidepressant medication in treating depression during pregnancy [25]. A 2005 meta-analysis of RCTs of light therapy concluded that bright light treatment for nonseasonal depression is efficacious, with effect sizes equivalent to those in most antidepressant pharmacotherapy trials [26]. Light therapy can also enhance the effectiveness of other treatments [27].

Bright light early in the morning seems to be the most effective. In most trials of light therapy, the patient sits in front of a light box, exposed to 10,000 lux for 30 to 120 minutes daily. Trials comparing the effects of light boxes with outdoor activity (eg, 15–60 minutes of sunlight daily) and tanning booths are needed.

Nature

Recently, a new field of inquiry has emerged that explores the therapeutic effects of nature and the natural environment. Investigators have called this

field biophilia, which emphasizes the connection to our natural environment [28]. This field of study includes both natural settings alone and those combined with contact with animals. One recent study from the *British Medical Journal* [29] explored the value of swimming with dolphins, a variation of animal-assisted therapy, controlled for the beneficial effect of the natural setting. A significant positive effect with this approach was found for 30 adult patients who had mild to moderate depression after 2 weeks of treatment in this single-blind RCT.

Minimizing environmental toxins

Heavy metals (eg, lead and mercury) [30] and carbon monoxide poisoning are also associated with depressive symptoms [31,32]. Checking for toxins and eliminating them may help improve mood. The benefit is well documented with lead and carbon monoxide, but the value for other heavy metals remains a frontier of knowledge at this point.

One of the easiest ways to become depressed is to compare oneself with someone who is more attractive and intelligent, or in possession of more friends, toys, desirable food, or clothing, or has better transportation or housing. Exposure to television and other sources of marketing increases the likelihood that children and adolescents will make these comparisons. Furthermore, the ''If it bleeds, it leads'' philosophy in the media has resulted in a preponderance of negative, disheartening news on television. Removing televisions from children's rooms and sharply reducing the time the television is on may contribute to improved mood. The elimination of marketing to children (already in place in several European countries), as a result of advocacy, could also contribute to enhanced mental health. At home, children and families can practice ''appreciation audits,'' listing the elements in their lives for which they are grateful or keeping a daily journal of appreciation and kindness items (ie, ways the writer has been kind to others). (For more information on the appreciation audit, see Dan Baker's book, listed in Appendix 1).

Poverty and lack of opportunity adversely affect mood [33,34]. Racism, sexism, homophobia, and other social injustices also contribute to suffering and decreased access to care [35–39]. Problems within the family and local community, such as child abuse and neglect and child sexual abuse have significant long-term adverse effects on mood [40–42]. Physician advocacy for social justice, equal access to care, and family support services can have a profound impact on children's moods.

Mind–body therapies

Meditation

Meditation practice, particularly mindfulness meditation (moment-to-moment nonjudgmental awareness of breathing, physical sensations, emotions, and thoughts), can contribute to enhanced mood, and can change brain activation patterns in ways likely to support ongoing benefits.

Specifically, meditation training leads to significant increases in left-sided anterior activation, a pattern associated with positive affect [43]. Long-term meditators, compared with age-matched controls, exhibit increased cortical thickness in brain regions associated with attention and sensory processing, including the prefrontal cortex [44]. Side effects of meditation may include improved ability to cope with stress, reduced pain, reduced anxiety, and enhanced immune function.

Dialectic behavior therapy

Dialectic behavior therapy is a psychosocial therapy based in cognitive behavioral therapy and mindfulness. Originally designed for chronically suicidal patients with borderline personality disorder, dialectic behavior therapy helps people build awareness about their emotional states and about how to gain control over behavior. This technique works well for emotionally labile teens with mood issues and for chronically suicidal teens [45,46]. Recently, one preliminary study [47] found benefits in children with oppositional defiant disorder (who commonly have comorbid mood disorders). A 1-year open trial with bipolar youth also found promising beneficial effects [48].

Eye movement desensitization and reprocessing

Eye movement desensitization and reprocessing (EMDR) significantly improved depression in adult patients of childhood sexual abuse in an RCT of 880 patients [49]. In this study, EMDR was most effective for more recent trauma and significantly outperformed fluoxetine on various measures. Many clinicians who treat children are finding EMDR a safe, effective, and often faster treatment approach for angry, violent, or depressed youth who have suffered abuse.

Other

Various evidenced-based approaches that calm the mind may play a role in the care of children with mood disorders. Tai chi and mindfulness techniques have been applied successfully in a Boston public middle school [50] and resulted in the improvement of various measures, including general well-being. Gordon and colleagues [51] applied various mind–body techniques to improve symptoms in a group of war-weary Kosovo students. Music therapy improved mood and depressive scales in a group of grieving children [52]. In an RCT of 69 adult patients hospitalized for stem cell transplantation, music therapy significantly improved mood and anxiety [53]. In a study of 22 children with recurrent abdominal pain (commonly comorbid with depression), guided imagery was a more effective treatment than breathing exercises alone [54]. Reynolds and Coats [55] demonstrated in an RCT that relaxation therapy was as effective as cognitive behavior therapy (a well-researched, evidence-based treatment) for a group of 30 depressed adolescents. Relaxation therapy was also found to be more effective than antidepressant therapy for major depression in one adult trial [56].

Social support and spirituality

Children who attend church regularly have about a 20% lower risk of developing depression than nonattendees. Church may be protective because of inherent spiritual factors and because it provides a sense of social support and cohesiveness and opportunities for connecting with a trusted adult in whom to confide. Numerous studies document benefit from various spiritual paths. The positive factors seem to be faith and community, rather than a specific belief system. Primary care clinicians can also provide important psychosocial support that improves outcomes in depressed adolescents [57].

Biochemical therapies

Because of our individual uniqueness (genomic variability), diet, and environment, some individuals require additional nutrients or benefit from specific biochemical therapies to achieve healthy moods. For example, simple nucleotide polymorphisms represent a significant factor in biochemical individuality. The enzyme delta-5-desaturase converts omega-3 fatty acids such as alpha linolenic acid into eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). If a simple nucleotide polymorphism impairs delta-5-desaturase, a child may require significantly higher levels of alpha linolenic acid, EPA, or DHA in his/her diet to maintain normal cell membrane function and healthy mood.

For this article, the authors focus on vitamins and minerals, herbs, and other dietary supplements. Given the fact that fewer than 1% of American children meet their recommended daily allowance of essential nutrients through diet alone [58], it is likely that many children would benefit from supplementation, in addition to striving to improve their overall diet. Supplementation is especially important for children who eat a restricted diet because of suspected food allergies or sensitivities. Also, any child who restricts calories, whether because he/she performs in such sports as wrestling, gymnastics, and so forth, or because he/she has self-image problems (ie, anorexia), will have enhanced needs. (Stress and conflict also significantly escalate nutrient demands).

Essential nutrients (vitamins, minerals, fatty acids, amino acids)

Here, the authors do not cover all essential nutrients, but focus on a few that are vitally important and often lacking in Americans, some of whom might benefit from nutrient supplementation.

Multivitamin–mineral preparations

Several investigators have concluded that multivitamin–mineral combinations can help improve mood and behavior. In a large British trial in 231 young offenders, violent acts and rule infractions were significantly reduced among those given micronutrient supplementation [59]. Several case

studies and case series support the effectiveness of a proprietary multivitamin–mineral (EMPower) on young people with mood disorders (including depression and bipolar disorders) [60–62]. This product has numerous testimonials, but requires up to 15 capsules daily for a loading dose; it contains significant amounts of calcium, magnesium, and B vitamins. It has not been compared with supplementation with generic versions of these nutrients.

Individual vitamins

B vitamins, including folate

Vitamin B_6 is essential in metabolizing tryptophan to serotonin. Folate and vitamin B_{12} are major determinants of one-carbon metabolism, in which S-adenosylmethionine (SAMe, pronounced Sam-ee) is formed. SAMe donates methyl groups that are crucial for neurologic function. See later discussion on SAMe.

Low levels of pyridoxal phosphate are significantly associated with depressive symptoms [63]. A systematic review suggested that 100 to 200 mg daily supplementation with vitamin B_6 significantly benefits premenstrual depression [64]. The side effects of excessive doses of vitamin B_6 include nausea, vomiting, abdominal pain, anorexia, headache, somnolence, lower B12 levels, and sensory neuropathy. The last typically occurs with doses of more than 1000 mg daily, but can occur lower with lower doses.

Folate is a water-soluble vitamin that donates a methyl group in the one-carbon cycle needed for the production of SAMe and the remethylation of homocysteine. Folate deficiency is common and contributes to various psychiatric symptoms, including depression, psychosis, irritability, dementia, and impaired memory.

Considerable research evidence supports the value of folate in maintaining a healthy mood. Folate and B12 levels are lower in depressed than in nondepressed persons, and replacing deficient folate can lead to remarkable improvements in mood [65–67]. Low folate levels predict treatment resistance to fluoxetine [68]. In one study, folate supplementation was as effective as 150 mg of amitriptyline in treating depressed outpatients [69]. Adding 500 μg of folate to 20 mg of fluoxetine significantly improved the response rate in patients who had major depression [70]. One review concluded that folate supplementation is beneficial in treating depression, whether used as monotherapy or as an augmentation of conventional medications [71]. Primary care clinicians should ensure that children prone to mood disorders have an adequate intake of folate and should consider recommending a multivitamin or a B-vitamin complex containing folate. Given the safety of water-soluble vitamins, a dose of 1 mg per day in symptomatic children is reasonable. It should be given with B_{12} to avoid masking a B_{12} deficiency.

Vitamin D

A growing body of research suggests that American youth are vitamin D–deficient, even in older pediatric and adolescent populations that do

not appear to have classic rickets [72–74]. This deficiency may be a particular problem in children taking anticonvulsant medications [75]; those with inflammatory bowel disease [76,77] or arthritis [78,79]; those with chronic renal disease [80]; those living in the inner city [81]; African-Americans [82]; or those who are veiled. Many adolescents have relatively low levels of vitamin D because of an indoor lifestyle and inadequate intake of vitamin D–fortified foods [83]. A recent study found that obese children have significantly depressed vitamin D levels [84], perhaps from inadequate outdoor time. Skin cancer concerns, inactivity, obesity, excessive screen time (eg, too much time watching television, playing electronic games, or working on a computer), and other issues may contribute to sun avoidance and vitamin D deficiency.

Low levels of vitamin D are associated with depressive symptoms, and treatment with vitamin D supplements is associated with improved mood. For example, 25-hydroxyvitamin D_3 and 1,25-dihydroxvitamin D_3 levels are significantly lower in psychiatric patients than in normal controls [85]. Vitamin D deficiency is associated with anxiety and depression in patients who have fibromyalgia [86]. In an RCT of vitamin D given to 44 Australian patients (none versus 400 IU versus 800 IU vitamin D), vitamin D_3 significantly enhanced mood in a dose-dependent fashion [87].

The recommended daily allowance for vitamin D was set to prevent rickets in young children and may be insufficient to prevent certain health problems in older adults. It may be worthwhile for adolescents to take vitamin D supplements, particularly during winter months, to ensure adequate vitamin D levels and prevent subclinical hypoparathyroidism; supplementation is also worthwhile for patients who have renal disease, inflammatory bowel disease, or juvenile arthritis, and those patients on anticonvulsant drugs that lower vitamin D levels.

Minerals

This section includes brief discussions on the role of calcium, magnesium, chromium, zinc, and iron in promoting and maintaining a healthy mood.

Calcium

Lower levels of calcium and higher levels of parathyroid hormone have been observed in depressed persons. Likewise, depression is commonly noted among patients suffering from hyperparathyroidism [88]. Quality of life and depressive symptoms improve when these patients receive appropriate treatment [89]. Estrogen regulates calcium and parathyroid hormone metabolism [90]; sometimes dysregulation occurs, which is particularly notable in women suffering from premenstrual symptoms. Epidemiologically, normal to high intakes of calcium and vitamin D are associated with a lower risk of depressive mood in patients who have premenstrual syndrome; conversely, lower intakes of calcium and vitamin D are associated with an increased risk of premenstrual syndrome [91]. Small studies suggest that

calcium supplementation may benefit women with premenstrual syndrome-related depression [92,93].

Most adolescent girls do not meet their minimum daily requirement for calcium through diet alone. According to the Continuing Survey of Food Intakes of Individuals (1994-96), the following percentages of Americans do not meet their recommended intake for calcium:

- 44% of boys and 58% of girls aged 6 to 11
- 64% of boys and 87% of girls aged 12 to 19

It is important for clinicians counseling adolescents about mood to address adequate calcium intake (optimally 1200–1500 mg daily) to ensure bone health and promote a healthy mood.

Magnesium

Magnesium is second only to potassium in intracellular concentration. It facilitates the conversion of 5-hydroxytryptophan (5-HTP) into serotonin. Signs of magnesium deficiency include irritability, fatigue, loss of appetite, mental confusion, insomnia, and a predisposition to stress. Historically, magnesium has been used, like lithium, as a treatment for mania or severe agitation [94]. It is not used widely or recommended as a treatment for depression.

Magnesium, like lithium, suppresses hippocampal kindling, regulates N-methyl-D-aspartate receptors, and alters glutamate activity [95,96]. It has been a successful treatment for premenstrual mood changes [97]. Magnesium and verapamil were much more effective than verapamil alone in treating acute mania [98].

Magnesium deficiency is extremely common [99]. Research is currently underway on the value of magnesium supplementation in pediatric bipolar disorder. Ensuring an adequate intake of magnesium is important in maintaining a balanced mood.

Chromium

Chromium, a dietary trace mineral, has a crucial role in glucose and fat metabolism and neurotransmitter synthesis. Chromium improves insulin sensitivity and increases free brain levels of serotonin, norepinephrine, and melatonin. In an RCT of bipolar II patients and patients who had atypical depression, chromium had a significant benefit [100]. Five patients responded to chromium supplementation after failing conventional depression treatment [101]. An RCT of chromium picolinate (600 μg daily) in patients whose depression was characterized by carbohydrate craving showed significant improvement in craving and depressive symptoms [102].

Chromium is well tolerated but can have a stimulating effect. The recommended daily allowance for chromium is 120 μg. The daily dietary intake of chromium for a typical American adult is only 25 to 50 μg per day. The dose range in studies of its effects on mood is typically 200 to 600 μg per day.

Dietary sources rich in chromium include breads, cereals, spices, fresh vegetables, meats, fish, and brewer's yeast.

Zinc

Zinc is an essential mineral that is found in almost every cell. It stimulates the activity of approximately 100 enzymes. Low serum zinc levels have been linked to major depression. Zinc, an antagonist of the glutamate/N-methyl-D-aspartate receptor, exhibits antidepressant-like activity in rodent models of depression. Like antidepressants, zinc induces brain-derived neurotrophic factor gene expression and increases the level of the synaptic pool of zinc in the hippocampus [103]. Furthermore, zinc treatment has been shown to have an antidepressant effect [104].

The American recommended dietary allowance for zinc ranges from 5 mg daily for younger children to 11 mg daily for teenagers. Vegetarians may need as much as 50% more zinc than nonvegetarians because of the lower absorption of zinc from plant foods, so it is important for vegetarians to include good sources of zinc in their diet. Breastfeeding depletes zinc, and some experts suggest that because breast milk contains relatively low levels of zinc, breastfed infants should receive zinc supplementation after 7 months of age.

Low zinc status has been observed in 30% to 50% of alcoholics. Alcohol decreases the absorption of zinc and increases the loss of zinc in urine. In addition, many alcoholics do not eat an acceptable variety or amount of food, so their dietary intake of zinc may be inadequate. If an adolescent has a drinking problem in addition to a mood problem, it is especially important to ensure adequate mineral supplementation.

Zinc toxicity occurs with intakes of 150 to 450 mg of zinc per day and appears as low copper status, altered iron function, reduced immune function, and reduced levels of high-density lipoproteins.

Iron

Iron deficiency anemia is often accompanied by depression. Long-term iron deficiency in infancy and early childhood is associated with mood and learning problems, even years after the deficiency is corrected [105]. It is important to ensure that adolescents be checked for iron sufficiency, particularly female adolescents who may not be meeting their needs for iron to replace menstrual losses [106]. Primary care clinicians should ensure that their patients consume adequate amounts of iron through either diet or supplementation.

Fatty acids

Linolenic, eicosapentaenoic, and docosahexaenoic acids

The human brain is 60% fat, and the essential fatty acids contribute a substantial portion of that weight. Essential fatty acids are crucial to normal fetal and neonatal maturation of the brain. Three common essential fatty acids (EPA, DHA, and arachidonic acid), are crucial building blocks

of neuronal membranes. Fatty acids also form the precursors of prostaglandins and leukotrienes. Fatty fish such as salmon, mackerel, and herring are excellent sources of EPA and DHA.

Fish consumption and levels of omega-3 fatty acids have a strong epidemiologic correlation with protection from depression and suicide [107–111]. Furthermore, clinical trials suggest that supplemental essential fatty acids (EPA and DHA) can improve mood and decrease hostility and violence, even in patients hospitalized for severe depression or suicidality [112–115]. The doses in these studies range from 1 g per day to 10 g per day.

The benefit of omega-3 supplementation for bipolar disorder is less clear [116]. Stoll and colleagues' [117] double-blind study augmenting treated bipolar patients with fish oil (9.6 g per day) or placebo found significant reductions in relapse and all other outcome measures with fish oil. However, another trial with 120 bipolar patients found no significant treatment effect [118]. A 2007 study of pediatric bipolar disorder [119] found a modest, but statistically significant, improvement in an open-label trial of 20 children, 6 to 17 years of age. The intervention was 1290 to 4300 mg of an EPA–DHA combination.

In children, the developmental requirements and absence of serious toxicity suggest that daily supplementation with 1 to 3 g of fish oil (EPA–DHA) can support healthy mood. Product testing has revealed no significant contamination with mercury, dioxins, or other contaminants in molecularly distilled fish oil products. More potent and palatable forms of molecularly distilled fish oils make these dietary recommendations easier to swallow. Small children can take one of the liquid forms often easily hidden in food. Recently, a prescription brand of fish oil entered the scene, further increasing treatment options.

Amino acids

L-tryptophan

5-HTP is the immediate precursor of serotonin in its metabolism from dietary L-tryptophan (L-trp). Unlike tryptophan, which faces competitive inhibition in its absorption, 5-HTP does not, and it appears to be a better choice for increasing central nervous system levels of serotonin.

Tryptophan depletion leads to depressive symptoms in rats and humans. Various smaller (open and controlled) studies [120–125] have found 5-HTP useful in depression. A Cochrane meta-analysis of trials involving 64 patients suggested 5-HTP and L-trp are better than placebo in treating depression [126]. The doses given in most trials start at 50 mg three times a day. The typical dosing is 50 mg, slowly increasing to 150 mg, two or three times daily on an empty stomach, based on size. A large single dose of 200 to 400 mg can be used by slowly increasing the dose. The maximum recommended dose is 1200 mg daily.

Side effects of 5-HTP and L-trp include nausea and drowsiness (which may make it useful at bedtime); they may cause serotonergic syndrome if

used in combination with selective serotonin reuptake inhibitor (SSRI) medications; they may also be associated with decreased carbohydrate intake and weight loss [127]. Eosinophilia-myalgia syndrome was reported in numerous people taking L-trp, which led to its removal from the American market; however, investigations revealed that the problem was related to a contaminated lot from one manufacturer, and L-trp is again available. During the time it was off the market, many people turned to 5-HTP supplements instead to ensure safety. Experts now recommend using products that are tested and free of a ''Peak X'' contaminant.

S-Adenosylmethionine

SAMe is a methyl donor in more than 35 reactions in the brain and body. It plays a crucial role in the production of monoamine neurotransmitters, nucleotides, and neuronal membrane phospholipids. SAMe has been found to be the most potent chemical trigger for the induction of mania in bipolar patients, a reflection of its antidepressant potency.

More than 25 controlled trials have evaluated the effectiveness of SAMe for patients with mood disorders. A 2002 review by the Agency for Health care Quality and Research (AHRQ) concluded that, compared with placebo, 3 weeks of treatment with SAMe was associated with a significant improvement in depression [128]. Several studies published since the AHRQ 2002 report confirm its effectiveness in improving mood, and suggest it has a potency similar to tricyclic antidepressants [129–132]. It may also be helpful in patients for whom antidepressant medications have been ineffective [133]. Furthermore, it can also be a useful adjunctive treatment, along with conventional antidepressant medications [133].

Typical doses are 800 to 1600 mg of SAMe daily. Benefits typically appear within 2 weeks of starting the medication. Although product variability is a major problem in many dietary supplements, a review of SAMe products by ConsumerLabs revealed that only 1 out of 11 tested products failed their rigorous standards.

SAMe has fewer side effects than conventional antidepressant medications and works more quickly. Side effects include triggering mania and increasing the risk of serotonergic syndrome in patients taking SSRI medications. It should not be used by patients who have bipolar disorder. Furthermore, it is expensive (50 cents to $1 per 200 mg tablet) and is not usually covered by insurance.

Herbs for mood

St. John's wort

The herb most commonly used as a complementary or alternative remedy for depression is St. John's wort. Studies on its effectiveness have had mixed results, with most of the positive studies coming from European trials using standard extracts [134]. See Table 3 for a listing of the compounds used in the studies with positive results and the American imports containing these

Table 3
St. John's wort products used in studies reporting positive effects

Products with positive results in clinical studies	Brand name (manufacturer)
LI 160 and LI 160S	Quanterra Emotional Balance (Warner-Lambert); Kira (Lichtwer Pharma US/Germany)
WS 5570 and WS 5572	Neuroplant (Schwabe Pharmaceuticals) Perika (Schwabe Pharmaceuticals, imported by Nature's Way Products, Inc)
Ze 117	Remotiv (Bayer Vital GmbH and Zeller AG)

Courtesy of Paula Gardiner, MD, Boston, MA.

compounds. For example, in a German RCT, St. John's wort was as effective as sertraline in improving depressive symptoms [135]. A similar German study showed its comparability to citalopram [136]. Two open-label trials in adolescents showed improvement within 2 weeks in 25 out of 33, and 9 out of 11 patients in separate studies [137,138]; patients who improved in these studies generally showed improvement within 2 weeks of starting therapy. It is reasonable to stop treatment or change to a higher dose or a different product if no benefit has been noted within 3 weeks.

St. John's wort is generally safer than most antidepressant medications. A meta-analysis of 16 post-marketing surveillance studies including 34,804 patients recorded an incidence of adverse events between 0% and 6%; of the four large-scale surveillance studies with a total of 14,245 patients, the rate of adverse events ranged from 0.1% to 2.4% and a drop-out rate due to adverse events of 0.1% to 0.9% [139]. This finding is at least ten-fold lower than that recorded with synthetic antidepressants. The adverse events associated with St. John's wort were mild and transient in nearly all cases.

St. John's wort can, however, have direct adverse effects and serious interactions with commonly used medications. The most common direct effects are phototoxicity and stomach upset. The most serious adverse effects are drug interactions in which St. John's wort reduces the serum levels of other medications including contraceptives, digoxin, immunosuppressants, theophylline, clarithromycin, erythromycin, cyclosporine, tacrolimus, protease inhibitors, and certain chemotherapeutic agents. It should not be used in conjunction with SSRIs because such use may increase the risk of serotonergic syndrome.

St. John's wort preparations have substantial variability in quality. Patients who wish to use it may use a product tested in a large RCT or refer to product testing conducted by ConsumerLabs (see Appendix 1).

Other dietary supplements

Inositol

Inositol, an isomer of glucose, works as an intracellular messenger that relays the neurotransmitter message to the cell nucleus. One review found

that inositol was useful in panic disorder, obsessive-compulsive disorder, and depression [140]. In a large comparative study of treatments for bipolar depression, the recovery rate was 23.8% for lamotrigine, 4.6% for risperdone, and 17.4% for inositol [141]. It has been suggested that inositol can trigger mania episodes in patients who have bipolar disorder [142]. Inositol can be mildly sedating and has also been used as a sleep aid. Inositol had far fewer side effects in all comparison studies. As a sweet-tasting powder that can be mixed into any liquid, inositol offers a well-tolerated intervention for children with mood disorders. The typical starting dose is 1 to 2 g two or three times daily, increasing up to 12 to 18 g per day in divided doses.

Biomechanical therapies: massage

Massage is used widely to improve mood. In fact, therapeutic massage struggles to overcome an historical connection with the "entertainment" industry. Despite its marketing problems, massage has many medical uses. Therapeutic massage contributes to increased blood flow and lymphatic drainage; muscle relaxation; stress reduction; and social support. Physiologically, massage balances right and left prefrontal cortex activity in those with right dominance [143]. The left prefrontal cortex has been associated with positive mood, whereas dominance of the right prefrontal cortex is associated with depressed mood [144]. Furthermore, massage decreases cortisol levels and increases levels of serotonin and dopamine in patients who have depression [145]. In depressed women, massage, compared with progressive relaxation, led to higher dopamine and serotonin levels and lower levels of cortisol and norepinephrine [146]. Massage significantly reduced aggression in 17 adolescent psychiatric inpatients [147]. A simple 30-minute back rub daily reduced anxiety and improved cooperation in 52 pediatric psychiatric inpatients [148].

Considerable research has been published on the pervasive and persistent negative effects of maternal depression on childhood mental health [149]. The infants of depressed mothers who received massage scored higher on various measures in the Brazelton scale than mothers who only received light touch [150], thus reducing the ensuing emotional risk to the unborn child.

In the studies showing positive effects, massage has generally been provided 5 days a week. To achieve this frequency cost effectively, parents are generally trained to provide massage for children and adolescents. Massage is generally safe if care is taken to avoid wounds, burns, intravenous lines, pumps or other subcutaneous devices, and vigorous strokes in patients who have low platelet counts. Careful discussion and respect for individual patients is important for patients who have a history of physical or sexual abuse.

Bioenergetic therapies: acupuncture

Acupuncture involves the stimulation (using pressure, heat, needles, and magnets) of specific points on the body, with the intention of promoting

healing. RCTs suggest that acupuncture has significant benefits for depressed adults and may be comparable in effectiveness to prescription antidepressant medications [151]. For example, in an RCT of true acupuncture, sham acupuncture, and massage provided to 61 pregnant women with major depressive disorder, response rates were statistically significantly higher for acupuncture (69%) than for massage (32%), with an intermediate sham acupuncture response rate (47%) [152]. In a meta-analysis published in 2005, the investigators concluded that "the effect of electroacupuncture may not be significantly different from antidepressant medication," with a weighted mean difference in comparison trials of −0.43 (95% CI −5.61 to 4.76) [153].

Acupuncture rarely causes bleeding, bruising, or infection; it causes sleepiness in about 5% of patients. In general, it has fewer side effects than medications. Serious side effects are rare. Pediatric patients will accept it, but it's not usually their first choice of therapies. Those who receive it generally report that it is helpful and, unlike their expectations, pleasant [154].

Resources

Research in this area is growing constantly. It is helpful to have a list of resources to address common questions and concerns and to keep abreast of emerging knowledge about the safety and effectiveness of therapies and approaches to promote healthy moods. See Appendix 1.

Summary

Depression is the second-leading cause of illness and disability among young people worldwide. A healthy lifestyle and healthy environment are the cornerstones for promoting positive moods. In addition, several complementary therapies, including nutritional supplements, herbs, mind–body therapies, massage, and acupuncture can be helpful. Various resources are available to clinicians to help patients and families promote mental health.

Appendix 1. Resources on integrative approaches to pediatric mood disorders

Internet resources

American Academy of Pediatrics Provisional Section for Complementary, Holistic and Integrative Medicine (http://www.aap.org/sections/chim/)

American Academy of Pediatrics, Committee on Environmental Health (http://www.aap.org/visit/cmte16.htm)

National Institutes of Health, Institute on Mental Health (information on depression in children and adolescents) (http://www.nimh.nih.gov/healthinformation/depchildmenu.cfm)

National Library of Medicine, Medline Plus (information on many medications, nutrients, and dietary supplements) (http://www.nlm.nih.gov/medlineplus/)
Natural Medicines Comprehensive Database (http://www.naturaldatabase.com/)
Natural Standard (http://www.naturalstandard.com/)
World Health Organization (information on depression) (http://www.who.int/mental_health/management/depression/definition/en/)
ConsumerLabs (comparison of dietary supplement brands) (www.consumerlabs.com)

Books

Baker D. What happy people know: how the new science of happiness can change your life for the better. New York: St. Martin's Press; 2003.
Baumel S. Dealing with depression naturally. Los Angeles (CA): Keats Publishing; 2000.
Emmons H. The chemistry of joy. New York: A Fireside Book (Simon and Schuster); 2006.
Hallowell EM. The childhood roots of adult happiness: five steps to help kids create and sustain lifelong joy. New York: Ballantine Books; 2002.
Lake J. Textbook of integrative mental health. New York: Thieme Medical Publishers; 2007.
Lake JH; Spiegel D. Complementary and alternative treatments in mental health care. Washington, DC: American Psychiatric Publishing; 2007.
Larson JM. Depression-free naturally. New York: Ballantine Books (Random House); 1999.
Shannon S, ed. Handbook of complementary and alternative therapies in mental health. San Diego (CA): Academic Press (Elsevier); 2001.
Shannon S. Please don't label my child. New York: Rodale Press; 2007.
Werbach MR. Nutritional influences on mental illness: a sourcebook of clinical research. Tarzana (CA): Third Line Press, Inc; 1999.
Williams M, Teasdale J, Segal Z, et al. The mindful way through depression: freeing yourself from chronic unhappiness. New York: Guilford Press; 2007.

References

[1] Murray L, Hipwell A, Hooper R, et al. The cognitive development of 5-year-old children of postnatally depressed mothers. J Child Psychol Psychiatry 1996;37(8):927–35.
[2] Birmaher B, Arbelaez C, Brent D. Course and outcome of child and adolescent major depressive disorder. Child Adolesc Psychiatr Clin N Am 2002;11(3):619–37, x.
[3] Zalsman G, Brent DA, Weersing VR. Depressive disorders in childhood and adolescence: an overview: epidemiology, clinical manifestation and risk factors. Child Adolesc Psychiatr Clin N Am 2006;15(4):827–41, vii.

[4] Kowatch RA, Fristad M, Birmaher B, et al. Treatment guidelines for children and adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 2005;44(3):213–35.
[5] Pavuluri MN, Birmaher B, Naylor MW. Pediatric bipolar disorder: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 2005;44(9):846–71.
[6] Grzywacz JG, Suerken CK, Quandt SA, et al. Older adults' use of complementary and alternative medicine for mental health: findings from the 2002 National Health Interview Survey. J Altern Complement Med 2006;12(5):467–73.
[7] Afifi M. Positive health practices and depressive symptoms among high school adolescents in Oman. Singapore Med J 2006;47(11):960–6.
[8] Hamre HJ, Witt CM, Glockmann A, et al. Anthroposophic therapy for chronic depression: a four-year prospective cohort study. BMC Psychiatry 2006;6:57.
[9] Ludwig DS. Clinical update: the low-glycaemic-index diet. Lancet 2007;369(9565):890–2.
[10] Kleinman RE, Hall S, Green H, et al. Diet, breakfast, and academic performance in children. Ann Nutr Metab 2002;46(Suppl 1):24–30.
[11] Fulkerson JA, Sherwood NE, Perry CL, et al. Depressive symptoms and adolescent eating and health behaviors: a multifaceted view in a population-based sample. Prev Med 2004; 38(6):865–75.
[12] Allgower A, Wardle J, Steptoe A. Depressive symptoms, social support, and personal health behaviors in young men and women. Health Psychol 2001;20(3):223–7.
[13] Bangash SA, Bahna SL. Pediatric food allergy update. Curr Allergy Asthma Rep 2005;5(6): 437–44.
[14] Bischoff SC. Role of mast cells in allergic and non-allergic immune responses: comparison of human and murine data. Nat Rev Immunol 2007;7(2):93–104.
[15] Teufel M, Biedermann T, Rapps N, et al. Psychological burden of food allergy. World J Gastroenterol 2007;13(25):3456–65.
[16] Christie L, Hine RJ, Parker JG, et al. Food allergies in children affect nutrient intake and growth. J Am Diet Assoc 2002;102(11):1648–51.
[17] Brown RS. Exercise and mental health in the pediatric population. Clin Sports Med 1982; 1(3):515–27.
[18] Anton SD, Newton RL Jr, Sothern M, et al. Association of depression with body mass index, sedentary behavior, and maladaptive eating attitudes and behaviors in 11 to 13-year old children. Eat Weight Disord 2006;11(3):e102–8.
[19] Hulens M, Vansant G, Claessens AL, et al. Health-related quality of life in physically active and sedentary obese women. Am J Hum Biol 2002;14(6):777–85.
[20] Pilkington K, Kirkwood G, Rampes H, et al. Yoga for depression: the research evidence. J Affect Disord 2005;89(1–3):13–24.
[21] Tsuno N, Besset A, Ritchie K. Sleep and depression. J Clin Psychiatry 2005;66(10):1254–69.
[22] Beauchemin KM, Hays P. Sunny hospital rooms expedite recovery from severe and refractory depressions. J Affect Disord 1996;40(1–2):49–51.
[23] Manuel JS. Solar flair. Environ Health Perspect 2003;111(2):A104–7.
[24] Lam RW, Levitt AJ, Levitan RD, et al. The Can-SAD study: a randomized controlled trial of the effectiveness of light therapy and fluoxetine in patients with winter seasonal affective disorder. Am J Psychiatry 2006;163(5):805–12.
[25] Epperson CN, Terman M, Terman JS, et al. Randomized clinical trial of bright light therapy for antepartum depression: preliminary findings. J Clin Psychiatry 2004;65(3): 421–5.
[26] Golden RN, Gaynes BN, Ekstrom RD, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. Am J Psychiatry 2005; 162(4):656–62.
[27] Martiny K. Adjunctive bright light in non-seasonal major depression. Acta Psychiatr Scand Suppl 2004;(425):7–28.
[28] Frumkin H. Beyond toxicity: human health and the natural environment. Am J Prev Med 2001;20(3):234–40.

[29] Antonioli C, Reveley MA. Randomised controlled trial of animal facilitated therapy with dolphins in the treatment of depression. BMJ 2005;331(7527):1231.
[30] Ross WD, Sholiton MC. Specificity of psychiatric manifestations in relation to neurotoxic chemicals. Acta Psychiatr Scand Suppl 1983;303:100–4.
[31] Schottenfeld RS, Cullen MR. Organic affective illness associated with lead intoxication. Am J Psychiatry 1984;141(11):1423–6.
[32] Johansson C, Castoldi AF, Onishchenko N, et al. Neurobehavioural and molecular changes induced by methylmercury exposure during development. Neurotox Res 2007; 11(3–4):241–60.
[33] Mikolajczyk RT, Bredehorst M, Khelaifat N, et al. Correlates of depressive symptoms among Latino and non-Latino white adolescents: findings from the 2003 California Health Interview Survey. BMC Public Health 2007;7:21.
[34] Galea S, Ahern J, Nandi A, et al. Urban neighborhood poverty and the incidence of depression in a population-based cohort study. Ann Epidemiol 2007;17(3):171–9.
[35] Siefert K, Finlayson TL, Williams DR, et al. Modifiable risk and protective factors for depressive symptoms in low-income African American mothers. Am J Orthopsychiatry 2007; 77(1):113–23.
[36] Igartua KJ, Gill K, Montoro R. Internalized homophobia: a factor in depression, anxiety, and suicide in the gay and lesbian population. Can J Commun Ment Health 2003;22(2): 15–30.
[37] Borrell LN, Kiefe CI, Williams DR, et al. Self-reported health, perceived racial discrimination, and skin color in African Americans in the CARDIA study. Soc Sci Med 2006;63(6): 1415–27.
[38] Whitbeck LB, McMorris BJ, Hoyt DR, et al. Perceived discrimination, traditional practices, and depressive symptoms among American Indians in the upper Midwest. J Health Soc Behav 2002;43(4):400–18.
[39] Szalacha LA, Erkut S, Garcia Coll C, et al. Discrimination and Puerto Rican children's and adolescents' mental health. Cultur Divers Ethnic Minor Psychol 2003;9(2):141–55.
[40] Salzinger S, Rosario M, Feldman RS, et al. Adolescent suicidal behavior: associations with preadolescent physical abuse and selected risk and protective factors. J Am Acad Child Adolesc Psychiatry 2007;46(7):859–66.
[41] Handwerker WP. Childhood origins of depression: evidence from native and nonnative women in Alaska and the Russian Far East. J Womens Health 1999;8(1):87–94.
[42] Widom CS, DuMont K, Czaja SJ. A prospective investigation of major depressive disorder and comorbidity in abused and neglected children grown up. Arch Gen Psychiatry 2007; 64(1):49–56.
[43] Davidson RJ, Kabat-Zinn J, Schumacher J, et al. Alterations in brain and immune function produced by mindfulness meditation. Psychosom Med 2003;65(4):564–70.
[44] Lazar SW, Kerr CE, Wasserman RH, et al. Meditation experience is associated with increased cortical thickness. Neuroreport 2005;16(17):1893–7.
[45] Rathus JH, Miller AL. Dialectical behavior therapy adapted for suicidal adolescents. Suicide Life Threat Behav 2002;32(2):146–57.
[46] Katz LY, Cox BJ, Gunasekara S, et al. Feasibility of dialectical behavior therapy for suicidal adolescent inpatients. J Am Acad Child Adolesc Psychiatry 2004;43(3): 276–82.
[47] Nelson-Gray RO, Keane SP, Hurst RM, et al. A modified DBT skills training program for oppositional defiant adolescents: promising preliminary findings. Behav Res Ther 2006; 44(12):1811–20.
[48] Goldstein TR, Axelson DA, Birmaher B, et al. Dialectical behavior therapy for adolescents with bipolar disorder: a 1-year open trial. J Am Acad Child Adolesc Psychiatry 2007;46(7): 820–30.
[49] van der Kolk BA, Spinazzola J, Blaustein ME, et al. A randomized clinical trial of eye movement desensitization and reprocessing (EMDR), fluoxetine, and pill placebo in the

treatment of posttraumatic stress disorder: treatment effects and long-term maintenance. J Clin Psychiatry 2007;68(1):37–46.
[50] Wall RB. Tai Chi and mindfulness-based stress reduction in a Boston public middle school. J Pediatr Health Care 2005;19(4):230–7.
[51] Gordon JS, Staples JK, Blyta A, et al. Treatment of posttraumatic stress disorder in post-war Kosovo high school students using mind-body skills groups: a pilot study. J Trauma Stress 2004;17(2):143–7.
[52] Hilliard RE. The effects of music therapy-based bereavement groups on mood and behavior of grieving children: a pilot study. J Music Ther 2001;38(4):291–306.
[53] Cassileth BR, Vickers AJ, Magill LA. Music therapy for mood disturbance during hospitalization for autologous stem cell transplantation: a randomized controlled trial. Cancer 2003;98(12):2723–9.
[54] Weydert JA, Shapiro DE, Acra SA, et al. Evaluation of guided imagery as treatment for recurrent abdominal pain in children: a randomized controlled trial. BMC Pediatr 2006; 6:29.
[55] Reynolds WM, Coats KI. A comparison of cognitive-behavioral therapy and relaxation training for the treatment of depression in adolescents. J Consult Clin Psychol 1986; 54(5):653–60.
[56] Murphy WJ, Talmadge CL, Tubis A, et al. Relaxation dynamics of spontaneous otoacoustic emissions perturbed by external tones. I. Response to pulsed single-tone suppressors. J Acoust Soc Am 1995;97(6):3702–10.
[57] Stein RE, Zitner LE, Jensen PS. Interventions for adolescent depression in primary care. Pediatrics 2006;118(2):669–82.
[58] Munoz KA, Krebs-Smith SM, Ballard-Barbash R, et al. Food intakes of US children and adolescents compared with recommendations. Pediatrics 1997;100(3 Pt 1):323–9.
[59] Gesch CB, Hammond SM, Hampson SE, et al. Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young adult prisoners. Randomised, placebo-controlled trial. Br J Psychiatry 2002;181:22–8.
[60] Kaplan BJ, Simpson JS, Ferre RC, et al. Effective mood stabilization with a chelated mineral supplement: an open-label trial in bipolar disorder. J Clin Psychiatry 2001;62(12): 936–44.
[61] Popper CW. Do vitamins or minerals (apart from lithium) have mood-stabilizing effects? J Clin Psychiatry 2001;62(12):933–5.
[62] Simmons M. Nutritional approach to bipolar disorder. J Clin Psychiatry 2003;64(3):338 [author reply 338–9].
[63] Hvas AM, Juul S, Bech P, et al. Vitamin B6 level is associated with symptoms of depression. Psychother Psychosom 2004;73(6):340–3.
[64] Wyatt KM, Dimmock PW, Jones PW, et al. Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: systematic review. BMJ 1999;318(7195):1375–81.
[65] Dimopoulos N, Piperi C, Salonicioti A, et al. Correlation of folate, vitamin B12 and homocysteine plasma levels with depression in an elderly Greek population. Clin Biochem 2007; 40(9–10):604–8.
[66] Tolmunen T, Voutilainen S, Hintikka J, et al. Dietary folate and depressive symptoms are associated in middle-aged Finnish men. J Nutr 2003;133(10):3233–6.
[67] Godfrey PS, Toone BK, Carney MW, et al. Enhancement of recovery from psychiatric illness by methylfolate. Lancet 1990;336(8712):392–5.
[68] Papakostas GI, Petersen T, Denninger JW, et al. Psychosocial functioning during the treatment of major depressive disorder with fluoxetine. J Clin Psychopharmacol 2004;24(5): 507–11.
[69] Bottiglieri T, Hyland K, Laundy M, et al. Folate deficiency, biopterin and monoamine metabolism in depression. Psychol Med 1992;22(4):871–6.
[70] Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial. J Affect Disord 2000;60(2):121–30.

[71] Crellin R, Bottiglieri T, Reynolds EH. Folates and psychiatric disorders. Clinical potential. Drugs 1993;45(5):623–36.
[72] Cashman KD. Vitamin D in childhood and adolescence. Postgrad Med J 2007;83(978): 230–5.
[73] Olmez D, Bober E, Buyukgebiz A, et al. The frequency of vitamin D insufficiency in healthy female adolescents. Acta Paediatr 2006;95(10):1266–9.
[74] Schnadower D, Agarwal C, Oberfield SE, et al. Hypocalcemic seizures and secondary bilateral femoral fractures in an adolescent with primary vitamin D deficiency. Pediatrics 2006; 118(5):2226–30.
[75] Bergqvist AG, Schall JI, Stallings VA. Vitamin D status in children with intractable epilepsy, and impact of the ketogenic diet. Epilepsia 2007;48(1):66–71.
[76] Pappa HM, Gordon CM, Saslowsky TM, et al. Vitamin D status in children and young adults with inflammatory bowel disease. Pediatrics 2006;118(5):1950–61.
[77] Sinnott BP, Licata AA. Assessment of bone and mineral metabolism in inflammatory bowel disease: case series and review. Endocr Pract 2006;12(6):622–9.
[78] Pepmueller PH, Cassidy JT, Allen SH, et al. Bone mineralization and bone mineral metabolism in children with juvenile rheumatoid arthritis. Arthritis Rheum 1996;39(5):746–57.
[79] Patel S, Farragher T, Berry J, et al. Association between serum vitamin D metabolite levels and disease activity in patients with early inflammatory polyarthritis. Arthritis Rheum 2007;56(7):2143–9.
[80] Khan S. Vitamin D deficiency and secondary hyperparathyroidism among patients with chronic kidney disease. Am J Med Sci 2007;333(4):201–7.
[81] Ford L, Graham V, Wall A, et al. Vitamin D concentrations in a UK inner-city multicultural outpatient population. Ann Clin Biochem 2006;43(Pt 6):468–73.
[82] Weng FL, Shults J, Leonard MB, et al. Risk factors for low serum 25-hydroxyvitamin D concentrations in otherwise healthy children and adolescents. Am J Clin Nutr 2007; 86(1):150–8.
[83] Calvo MS, Whiting SJ, Barton CN. Vitamin D fortification in the United States and Canada: current status and data needs. Am J Clin Nutr 2004;80(6 Suppl):1710S–6S.
[84] Reinehr T, de Sousa G, Alexy U, et al. Vitamin D status and parathyroid hormone in obese children before and after weight loss. Eur J Endocrinol 2007;157(2):225–32.
[85] Schneider B, Weber B, Frensch A, et al. Vitamin D in schizophrenia, major depression and alcoholism. J Neural Transm 2000;107(7):839–42.
[86] Armstrong DJ, Meenagh GK, Bickle I, et al. Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. Clin Rheumatol 2007;26(4):551–4.
[87] Lansdowne AT, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. Psychopharmacology (Berl) 1998;135(4):319–23.
[88] Bohrer T, Krannich JH. Depression as a manifestation of latent chronic hypoparathyroidism. World J Biol Psychiatry 2007;8(1):56–9.
[89] Roman S, Sosa JA. Psychiatric and cognitive aspects of primary hyperparathyroidism. Curr Opin Oncol 2007;19(1):1–5.
[90] Thys-Jacobs S. Micronutrients and the premenstrual syndrome: the case for calcium. J Am Coll Nutr 2000;19(2):220–7.
[91] Bertone-Johnson ER, Hankinson SE, Bendich A, et al. Calcium and vitamin D intake and risk of incident premenstrual syndrome. Arch Intern Med 2005;165(11):1246–52.
[92] Dickerson LM, Mazyck PJ, Hunter MH. Premenstrual syndrome. Am Fam Physician 2003;67(8):1743–52.
[93] Thys-Jacobs S, Ceccarelli S, Bierman A, et al. Calcium supplementation in premenstrual syndrome: a randomized crossover trial. J Gen Intern Med 1989;4(3):183–9.
[94] Heiden A, Frey R, Presslich O, et al. Treatment of severe mania with intravenous magnesium sulphate as a supplementary therapy. Psychiatry Res 1999;89(3):239–46.
[95] Siwek M, Wrobel A, Dudek D, et al. [The role of copper and magnesium in the pathogenesis and treatment of affective disorders]. Psychiatr Pol 2005;39(5):911–20 [in Polish].

[96] Murck H. Magnesium and affective disorders. Nutr Neurosci 2002;5(6):375–89.
[97] Facchinetti F, Sances G, Borella P, et al. Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium. Headache 1991;31(5):298–301.
[98] Giannini AJ, Nakoneczie AM, Melemis SM, et al. Magnesium oxide augmentation of verapamil maintenance therapy in mania. Psychiatry Res 2000;93(1):83–7.
[99] Schimatschek HF, Rempis R. Prevalence of hypomagnesemia in an unselected German population of 16,000 individuals. Magnes Res 2001;14(4):283–90.
[100] Davidson JR, Abraham K, Connor KM, et al. Effectiveness of chromium in atypical depression: a placebo-controlled trial. Biol Psychiatry 2003;53(3):261–4.
[101] McLeod MN, Gaynes BN, Golden RN. Chromium potentiation of antidepressant pharmacotherapy for dysthymic disorder in 5 patients. J Clin Psychiatry 1999;60(4):237–40.
[102] Docherty JP, Sack DA, Roffman M, et al. A double-blind, placebo-controlled, exploratory trial of chromium picolinate in atypical depression: effect on carbohydrate craving. J Psychiatr Pract 2005;11(5):302–14.
[103] Nowak G, Szewczyk B, Pilc A. Zinc and depression. An update. Pharmacol Rep 2005;57(6): 713–8.
[104] Levenson CW. Zinc: the new antidepressant? Nutr Rev 2006;64(1):39–42.
[105] Lozoff B, Jimenez E, Hagen J, et al. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics 2000;105(4):E51.
[106] Rangan AM, Blight GD, Binns CW. Iron status and non-specific symptoms of female students. J Am Coll Nutr 1998;17(4):351–5.
[107] Conklin SM, Harris JI, Manuck SB, et al. Serum omega-3 fatty acids are associated with variation in mood, personality and behavior in hypercholesterolemic community volunteers. Psychiatry Res 2007;152(1):1–10.
[108] Garland MR, Hallahan B, McNamara M, et al. Lipids and essential fatty acids in patients presenting with self-harm. Br J Psychiatry 2007;190:112–7.
[109] Hibbeln JR. Fish consumption and major depression. Lancet 1998;351(9110):1213.
[110] Hibbeln JR. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. J Affect Disord 2002; 69(1–3):15–29.
[111] Silvers KM, Scott KM. Fish consumption and self-reported physical and mental health status. Public Health Nutr 2002;5(3):427–31.
[112] Hallahan B, Hibbeln JR, Davis JM, et al. Omega-3 fatty acid supplementation in patients with recurrent self-harm. Single-centre double-blind randomised controlled trial. Br J Psychiatry 2007;190:118–22.
[113] Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. Am J Psychiatry 2002;159(3): 477–9.
[114] Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. Arch Gen Psychiatry 2002;59(10):913–9.
[115] Su KP, Shen WW, Huang SY. Omega-3 fatty acids as a psychotherapeutic agent for a pregnant schizophrenic patient. Eur Neuropsychopharmacol 2001;11(4):295–9.
[116] Stoll AL, Locke CA, Marangell LB, et al. Omega-3 fatty acids and bipolar disorder: a review. Prostaglandins Leukot Essent Fatty Acids 1999;60(5–6):329–37.
[117] Stoll AL, Severus WE, Freeman MP, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. Arch Gen Psychiatry 1999;56(5): 407–12.
[118] Keck PE Jr, McElroy SL. Carbamazepine and valproate in the maintenance treatment of bipolar disorder. J Clin Psychiatry 2002;63(Suppl 10):13–7.
[119] Wozniak J, Biederman J, Mick E, et al. Omega-3 fatty acid monotherapy for pediatric bipolar disorder: a prospective open-label trial. Eur Neuropsychopharmacol 2007;17(6–7): 440–7.

[120] Alino JJ, Gutierrez JL, Iglesias ML. 5-Hydroxytryptophan (5-HTP) and a MAOI (nialamide) in the treatment of depressions. A double-blind controlled study. Int Pharmacopsychiatry 1976;11(1):8–15.
[121] Angst J, Woggon B, Schoepf J. The treatment of depression with L-5-hydroxytryptophan versus imipramine. Results of two open and one double-blind study. Arch Psychiatr Nervenkr 1977;224(2):175–86.
[122] Byerley WF, Judd LL, Reimherr FW, et al. 5-Hydroxytryptophan: a review of its antidepressant efficacy and adverse effects. J Clin Psychopharmacol 1987;7(3):127–37.
[123] Nolen WA, van de Putte JJ, Dijken WA, et al. L-5HTP in depression resistant to re-uptake inhibitors. An open comparative study with tranylcypromine. Br J Psychiatry 1985;147: 16–22.
[124] Turner EH, Loftis JM, Blackwell AD. Serotonin a la carte: supplementation with the serotonin precursor 5-hydroxytryptophan. Pharmacol Ther 2006;109(3):325–38.
[125] van Hiele LJ. l-5-Hydroxytryptophan in depression: the first substitution therapy in psychiatry? The treatment of 99 out-patients with 'therapy-resistant' depressions. Neuropsychobiology 1980;6(4):230–40.
[126] Shaw K, Turner J, Del Mar C. Tryptophan and 5-hydroxytryptophan for depression. Cochrane Database Syst Rev 2002;1:CD003198.
[127] Das YT, Bagchi M, Bagchi D, et al. Safety of 5-hydroxy-L-tryptophan. Toxicol Lett 2004; 150(1):111–22.
[128] AHRQ. S-Adenosyl-L-methionine for treatment of depression, osteoarthritis, and liver disease. In: AHRQ, editor. 2002. Available at: www.ahrq.gov/clinic/epcsums/melatsun.htm.
[129] Pancheri P, Scapicchio P, Chiaie RD. A double-blind, randomized parallel-group, efficacy and safety study of intramuscular S-adenosyl-L-methionine 1,4-butanedisulphonate (SAMe) versus imipramine in patients with major depressive disorder. Int J Neuropsychopharmacol 2002;5(4):287–94.
[130] Hardy ML, Coulter I, Morton SC, et al. S-adenosyl-L-methionine for treatment of depression, osteoarthritis, and liver disease. Evid Rep Technol Assess (Summ) 2003;64:1–3.
[131] Shippy RA, Mendez D, Jones K, et al. S-adenosylmethionine (SAM-e) for the treatment of depression in people living with HIV/AIDS. BMC Psychiatry 2004;4:38.
[132] Williams AL, Girard C, Jui D, et al. S-adenosylmethionine (SAMe) as treatment for depression: a systematic review. Clin Invest Med 2005;28(3):132–9.
[133] Alpert JE, Papakostas G, Mischoulon D, et al. S-adenosyl-L-methionine (SAMe) as an adjunct for resistant major depressive disorder: an open trial following partial or nonresponse to selective serotonin reuptake inhibitors or venlafaxine. J Clin Psychopharmacol 2004; 24(6):661–4.
[134] Linde K, Mulrow CD, Berner M, et al. St John's wort for depression. Cochrane Database Syst Rev 2005;2:CD000448.
[135] Gastpar M, Singer A, Zeller K. Efficacy and tolerability of hypericum extract STW3 in long-term treatment with a once-daily dosage in comparison with sertraline. Pharmacopsychiatry 2005;38(2):78–86.
[136] Gastpar M, Singer A, Zeller K. Comparative efficacy and safety of a once-daily dosage of hypericum extract STW3-VI and citalopram in patients with moderate depression: a double-blind, randomised, multicentre, placebo-controlled study. Pharmacopsychiatry 2006; 39(2):66–75.
[137] Findling RL, McNamara NK, O'Riordan MA, et al. An open-label pilot study of St. John's wort in juvenile depression. J Am Acad Child Adolesc Psychiatry 2003;42(8):908–14.
[138] Simeon J, Nixon MK, Milin R, et al. Open-label pilot study of St. John's wort in adolescent depression. J Child Adolesc Psychopharmacol 2005;15(2):293–301.
[139] Schulz V. Safety of St. John's wort extract compared to synthetic antidepressants. Phytomedicine 2006;13(3):199–204.
[140] Levine J. Controlled trials of inositol in psychiatry. Eur Neuropsychopharmacol 1997;7(2): 147–55.

[141] Nierenberg AA, Ostacher MJ, Calabrese JR, et al. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. Am J Psychiatry 2006;163(2):210–6.
[142] Levine J, Witztum E, Greenberg BD, et al. Inositol-induced mania? Am J Psychiatry 1996; 153(6):839.
[143] Jones NA, Field T. Massage and music therapies attenuate frontal EEG asymmetry in depressed adolescents. Adolescence 1999;34(135):529–34.
[144] Accortt EE, Allen JJ. Frontal EEG asymmetry and premenstrual dysphoric symptomatology. J Abnorm Psychol 2006;115(1):179–84.
[145] Field T, Hernandez-Reif M, Diego M, et al. Cortisol decreases and serotonin and dopamine increase following massage therapy. Int J Neurosci 2005;115(10):1397–413.
[146] Field T, Diego MA, Hernandez-Reif M, et al. Massage therapy effects on depressed pregnant women. J Psychosom Obstet Gynaecol 2004;25(2):115–22.
[147] Diego MA, Field T, Hernandez-Reif M, et al. Aggressive adolescents benefit from massage therapy. Adolescence 2002;37(147):597–607.
[148] Field T, Morrow C, Valdeon C, et al. Massage reduces anxiety in child and adolescent psychiatric patients. J Am Acad Child Adolesc Psychiatry 1992;31(1):125–31.
[149] Weissman MM, Wickramaratne P, Nomura Y, et al. Offspring of depressed parents: 20 years later. Am J Psychiatry 2006;163(6):1001–8.
[150] Field T, Hernandez-Reif M, Diego M. Newborns of depressed mothers who received moderate versus light pressure massage during pregnancy. Infant Behav Dev 2006;29(1):54–8.
[151] Leo RJ, Ligot JS Jr. A systematic review of randomized controlled trials of acupuncture in the treatment of depression. J Affect Disord 2007;97(1–3):13–22.
[152] Manber R, Schnyer RN, Allen JJ, et al. Acupuncture: a promising treatment for depression during pregnancy. J Affect Disord 2004;83(1):89–95.
[153] Mukaino Y, Park J, White A, et al. The effectiveness of acupuncture for depression–a systematic review of randomised controlled trials. Acupunct Med 2005;23(2):70–6.
[154] Kemper KJ, Sarah R, Silver-Highfield E, et al. On pins and needles? Pediatric pain patients' experience with acupuncture. Pediatrics 2000;105(4 Pt 2):941–7.