INTEGRATIVE APPROACHES TO PEDIATRIC MOOD DISORDERS

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Pediatric mood disorders (depression and bipolar disorders) represent common, serious, and recurrent medical illnesses. According to the World Health Organization, major depression now constitutes the number-one cause of illness related impairment in developed countries worldwide.[1] Naturally representative data from 15- to 17-year-olds in the United States indicate a prevalence rate of about 5% for major depression. The number of children and teens with milder forms of depression is probably about 8% to 10%.[2] Rates for pediatric bipolar disorder are much less clear but may represent about 1% of the teenage population.[3] A 2007 study showed that the rates of pediatric outpatient bipolar diagnosis rose 40-fold between 1994 and 2003.[4] Before puberty, the rates of mood disorder are higher in boys; after puberty, girls experience about twice the rates found in boys. Suicide rates for older teenagers represent a leading cause of death and an alarming tragedy.

This article will focus on the use of botanical and nutritional therapies in the integrative approach to pediatric mood disorders. Although the emphasis will be placed on evidenced-based approaches, the author recognizes the value of traditional practice and personal experience in this field where large well-designed and controlled studies are few. Given the huge level of consumer interest and increasing practitioner interest, guidance is clearly warranted. Given the enormous number of influences upon our mental and emotional health, this article will also emphasize the need for comprehensive understanding of the young person's world. Without this broad context, even the most evidence-based of treatments can be misguided or inappropriate.

A number of excellent reviews of the evidence base for integrative treatment in mental health exist.[5,6] Kaplan and Shannon published a review of nutritional approaches in mood disorder and in pediatric psychopharmacology.[7] Finally, a more comprehensive review of the range of treatment options in the pediatric mood disorders can be found in the article by Kemper and Shannon.[8]

Mood disorders in children and adolescents present a serious challenge for the practicing clinician. These internalizing disorders can be difficult to accurately identify and diagnose. There are many reasons why accurately identifying pediatric mood disorders can be so challenging.

First, children represent a moving target of symptom patterns. In some children, particularly younger boys, behavioral displays and angry dyscontrol may predominate, whereas in girls, withdrawal and isolation may more often predominate. At the younger end of the spectrum (in elementary school–aged children), there may be little ability to verbalize or identify sadness, yet many 15-year-olds can voice their inner turmoil.

Second, comorbidity is the rule in child and adolescent psychopathology. The typical symptomatic child evaluated by structured interviews will earn 3 separate diagnoses from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*). So merely correctly identifying the right primary mental health issue may not be enough. For example, more than one-third of children with attention-deficit-hyperactivity disorder will have a concomitant mood or anxiety disorder, and this will alter the ideal treatment algorithm.

Third, as internalizing disorders, we must gain entry into the child's inner world and assess the issues from the child's perspective. Many of the emotional and behavioral concerns that bring children and teens into the doctor's office can be judged using checklists and parent/teacher reports. This is not true with most mood disorders. We must gain the trust and communication necessary to hear the child's perspective.

Thus, the clinician must undertake a broad assessment of the whole child. A rapid, symptom-based, *DSM* criteria checklist approach to evaluation will not honor the ecology of the child or teen at hand. A comprehensive understanding of the range of influences, barriers, issues, concerns, deficiencies, misfits, excesses, and imbalances will guide practitioners toward the wisest approach.

One method to support broad holistic assessment of the whole child involves the use of a 6-realm template. In this model, we arbitrarily break the child's world down into 6 realms of existence. By covering this template with every assessment the practitioner will be assured of a more holistic assessment, thus enhancing the integrative treatment model. Many other templates exist; find one that works for you. The 6 realms are as follows:

- Environmental—water quality, air quality, noise, toxic load, crowding, economic stress;
- Physical—nutrition, sleep, exercise, gut;

- Mental—beliefs, attitudes, intellectual stimulation, creative expression;
- Emotional—parental support, trauma, conflict, self-esteem, forgiveness, bullying;
- Social—friendships, extended family, community; and
- Spiritual—values, purpose, religious path, gratitude, service.

This combination of holistic assessment and integrative treatment can be thought of as ecological care. Ecological care recognizes the myriad influences upon mental health and echoes the systems approach that now predominates in modern science. Sadly, modern psychiatry has veered back towards a reductionistic and mechanistic biochemical view of human existence. This narrow view of human nature does not accurately reflect the ecological nature of children. In an ecological approach, understanding the whole child and his or her world takes precedence over the selection of best treatment. In this view, the removal of barriers to healing should occur very early in treatment. Also, the use of multiple, simultaneous treatment influences for the young person makes more sense than a single, narrow, powerful influence. Finally, the ecological perspective honors the self-healing capacity of the child's ecosystem. This homeostatic force must remain clear in our view of each and every child.

THE CRUCIAL IMPORTANCE OF LIFESTYLE CHANGE

Lifestyle and mood issues are interwoven. Solid research links proper exercise, sleep, and stress management techniques to improved mental health and reduced mood related issues.[9,10] Though the scope of this article narrows to botanical and nutritional approaches, practitioners must hold these lifestyle issues in the foreground when creating a treatment plan. Often, appropriate lifestyle intervention will preclude the need for any additional specific treatment.

A recent review found that children and adolescents with major depression have a heightened risk for becoming obese.[11] Also, obesity is clearly associated with depressive disorder in females, and abdominal obesity is associated with depressive disorders in both females and males. A recent article proposes a link between the satiety hormone, leptin, obesity, and mood disorders.[12] It is too early to tell if our recent epidemics of pediatric obesity and pediatric mood disorders are linked, but the indicators are there.

NUTRIENTS AS MEDICINE

The link between specific nutrients and mood disorders is much more clear. Deficiencies of various B vitamins have been shown to cause brain dysfunction (Korsakoff Syndrome, pellagra, etc) and are linked to depression symptomology.[13] Bottigheri et al[14] found 52% of one sample of depressed patients had elevated homocysteine, indicative of low functional folate status.

Conversely, folate supplementation decreased clinical symptoms in a randomized controlled trial (RCT) of 41 patients.[15] Coppen and Bailey found that folate significantly increased the response rate of fluoxetine from 61% to 94% in women.[16]

Another link in the one carbon cycle, S-adenosyl-L-methionine (SAMe) has solid evidence as a treatment for major depression. Prior to 1996, 25 controlled studies evaluated the effectiveness of SAMe for treating major depression. Two meta-analyses of SAMe explored these studies. The first found SAMe to be far superior to placebo and outperformed conventional antidepressants.[17] Pancheri et al published a meta-analyses of SAMe in depression that used the Hamilton rating scale for response and enrollment.[18] In 4 of 6 studies examined, SAMe was found to have superior antidepressant response than placebo. All of these studies have found that side effects are much less and response time shorter than with conventional antidepressants. No studies have explored the value of SAMe in pediatric depression. SAMe is a potent trigger for manic cycling and should not be used in patients with a bipolar history or those with a family history of bipolar disorder.

Other nutritional interventions have been found to be helpful in treating mood disorders. Chromium has been found to be useful in treating atypical depression (characterized by hyperphagia, hypersomnia, and fatigue) in adults.[19] Magnesium reduced manic symptoms in 2 studies.[20,21]

Inositol, an isomer of glucose and part of our normal diet, benefited adults with unipolar and bipolar depression.[22,23] 5-HTP, a metabolite of L-tryptophan, a precursor of serotonin, effectively improved mood in adults with moderate depression.[24] L-tryptophan has good evidence; however, it is more complicated to use than 5-HTP and has more side effects.

Essential Fatty Acids

The child's brain triples in weight between birth and adulthood. The human brain is 60% fat, and the essential fatty acids (EFA) contribute a substantial portion of that weight gain. EFAs are crucial to normal fetal and neonatal maturation of the brain. Three common EFAs, eicosapentanoic acid (EPA), docasahexanoic acid (DHA), and arachidonic acid (AA), are crucial building blocks of phospholipid and neuronal membranes. Fatty acids also form the precursors of prostaglandins and leukotrienes, the body's principle regulatory molecules.

Worldwide epidemiological data has found strong correlations between fish consumption and a protection from depression and suicide.[25-27] A few laboratory studies have supported the hypothesis that depression is an inflammatory illness with alterations between the omega 3 (antiinflammatory) and omega 6 (proinflammatory) EFAs.[28,29]

In terms of treating depression with EFAs, the trials are more mixed. Three studies (all double-blind, placebo-controlled) demonstrated that EPA or EPA/DHA combinations resulted in significant improvement of depressed mood.[30-32] One small study found that DHA at a dose of 2 g per day did not separate from placebo.[33] The doses in these studies range from 1 g per day to 9.6 g per day. Stoll and other researchers believe that EPA is the more mood responsive form of omega-3 EFA, but clarification is needed.[34]

One recent study of EPA treatment of depression is of note. In this study, 28 children with major depression were randomized into either placebo or 1000 mg of fish oil containing 400 mg of EPA and 200 mg of DHA.[35] Seven of the 10 in the omega-3 group remitted,

whereas none of the placebo group responded.

With respect to bipolar disorder, the evidence is less clear. Stoll's[36] double-blind study augmenting treated bipolar patients with fish oil (9.6 g/day) or placebo found significant reductions in relapse and all other outcome measures. Another 4-month RCT with 120 bipolar patients found no separation from placebo.[37] In a recent study of pediatric bipolar disorder, Wozniak found a modest but statistically significant improvement in an open label trial of 20 children 6 to 17 years of age.[38] The intervention was 1290 to 4300 mg of EPA/DHA combination.

This is an area of intense and rapidly changing research. It is helpful to review the changing reach of this topic.[39-41] At this time, the data do not permit conclusive treatment recommendations for mood disorder. In children, however, the current developmental requirements and dietary recommendations in the absence of toxicity and consensus permit one to encourage supplementation of 1 to 3 g of fish oil (EPA/DHA) per day as prevention and possible treatment support. Studies have demonstrated no significant mercury issues in these supplements as small fish are used, thus avoiding the food chain issue. 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 our options.

Multi-ingredient Formulas

In 1994, the well-known nutrition researcher, Walter Mertz, contended that the narrow 1 disease/1 nutrient model was outdated.[42] He saw that narrow, single-nutrient interventions actually enhanced the risk of upsetting crucial metabolic balance and could create deficiencies of other nutrients. In animal nutrition, the concept of the first limiting nutrient teaches that every animal faces a gradient of potential nutritional deficiencies. Most human studies indicate that the average person has more than one nutrient deficiency. Simply correcting the greatest deficiency in a mix of deficiencies leaves the next most severe deficiency unaddressed. Multi-ingredient formulas best reflect nature and may be the most effective type of intervention. Modern medicine, however, hates the absence of a single variable.

The most notable evidence of this approach can be found in a series of 5 published papers on a food-based 36-ingredient formula for the treatment of unstable mood. On/off control of mood and aggression with this proprietary mix of minerals, vitamins, and trace elements was shown in 2 children who were followed for 4 years.[43] The same researchers documented effective intervention with large effect sizes in 2 open-label case studies. One of these was in children with anxiety and mood disorders[44] and another in adults with bipolar disorder.[45] Two psychiatrists describe similar response rates in clinical practice.[46,47] A larger RCT in adult bipolar patients is now underway. In an unrelated study, Gesch[48] reported on a large RCT of 231 young offenders who showed significant reductions in violent acts and rule infractions from a combination of vitamins, minerals, and essential fatty acids.

St John's Wort and Other Botanical Approaches

St John's wort (SJW) (*Hypericum perforatum*) grows as a perennial plant in Europe, Asia, and the United States. The traditional botanical use of this plant goes back to 2500 years to Hippocrates. Over the centuries, SJW has been used for a variety of uses both in mental health and for general medical issues. SJW is widely used in Europe as a first-line treatment for depression and outsells fluoxetine there.

Over the last 20 years, a large number of studies have been performed on SJW in the treatment of depression. A meta-analysis published in the *British Medical Journal* in 1996 evaluated 23 random trials (20 were double-blinded) of SJW in 1757 outpatients with mild-to-moderate depression.[49] In the 8 trials that compared SJW to tricyclic antidepressants, the outcomes were roughly equivalent but the side effect profile of SJW was quite superior (all side effects: 19.8% vs 52.8%). In the 15 placebo-controlled trials, SJW demonstrated significantly better clinical outcomes.

There have been 3 studies in children. In one open study of 101 children under the age of 12, the effectiveness of 300 to 1800 mg per day was evaluated in depression.[50] The percentage of children reaching the good or excellent response rating increased from 72% after 2 weeks to 97% at 4 weeks. By the end of the study, only 76% of the initial sample remained enrolled. In an open-label pilot study, 33 children aged 6 to 16 with major depression were given 150 mg 3 times daily, increasing to 300 mg 3 times daily if not responsive.[51] Twenty-five patients met response criteria at 8 weeks. SJW was well tolerated. Simeon et al evaluated the value of SJW in treating adolescents ages 12 to 17 with major depression in an open-label study.[52] Doses of SJW were 300 mg 3 times daily. Of the 26 patients enrolled, only 11 completed the 8-week study, and 9 of these showed a response. Of the 15 noncompleters, 8 were noncompliant, and 7 discontinued because of persisting illness.

Three recent studies have compared SJW with selective serotonin reuptaKe inhibitors in major depression in adults. In the first neither SJW nor sertraline separated from placebo.[53] In the second RCT,[54] 251 patients with major depression were treated with either 900 mg per day of hypericum or 20 mg per day of paroxetine. The intention to treat analysis showed noninferiority of hypericum and a statistical superiority over paroxetine. SJW was better tolerated. In the third RTC,[55] 135 patients with major depressive disorder were treated with 900 mg of hypericum or 20 mg per day of fluoxetine. SJW was significantly more effective than fluoxetine. A decreased sample size prevented separation from placebo.

All in all, a number of recent studies confirm the effectiveness if SJW in treating mild-to-moderate depression. Three small open-label studies indicate promise and safety in children. Three recent studies point to promising results in treating major depression. SJW is well tolerated with rare side effects of nausea, headache, or sun sensitivity. Doses are typically 300 mg of a standardized preparation (usually 0.3% hypericins) twice daily for smaller children (under 8) and 900 mg per day in 2 divided doses for children 9 and up. Avoid mixing with concomitant high dose SSRIs, as a serotonin syndrome has been reported. As with any antidepressant, avoid use in anyone with a bipolar type presentation, and use with caution in

anyone with a severe family history of bipolar disorder.

There are many other botanicals with appropriate use in pediatric mood disorders. However, the evidence base is quite lacking. Valerian root may play a role in sleep disturbances,[56] but at least study found enhanced benefit by combining it with a hops extract.[57] Kennedy found that *Melissa offcinalis* improved mood and calmness in a group of normal volunteers.[58] A recent rodent model finds that the lipophillic extract of the ginkgo leaf (commonly lost in commercial preparations) demonstrated significant antidepressant indicators.[59]

Rhodiola rosea grows in the foothills of Siberia. It has been used for centuries in Eastern Europe and Asia as a traditional treatment for stress and depression. One recent study confirms this application.[60] Given the known neuroendocrine abnormalities found in severe depression, Rhodiola may play a significant role in assisting the movement back to a healthy baseline.

SYMPTOM-BASED TREATMENT

In adult psychiatry, clinical reliability is fair when using cumbersome structured interview formats. In actual clinical practice, however, reliability remains poor.[61] Reliability in the clinical practice of child psychiatry is less than in adult psychiatry. Children are difficult to diagnose. They have high levels of comorbidity, shifting cognitive depth, and multiple developmental lines. For this and other reasons, it seems best to focus on symptom-based treatment. This approach downplays many of the negative consequences of labeling and allows practitioners to focus instead on strengths, barriers, triggers, and challenges.

Every practitioner must work to identify strengths for the child at hand. These strengths will help to pull them through tough times and propel them to success. Explore their world and identify any gifts or talents the child possesses. These can be academic, social, athletic, or musical. Ask about passions. If the young person is passionate about anything, this energy can be harnessed to their benefit. Our strengths enhance self-esteem and confidence.

In the assessment process, we must recognize barriers to health and wholeness. Barriers can be poor diet, lack of exercise, bullying, gut dysbiosis, poor fit with parent, or deficient sunlight (vitamin D). Spend time exploring for barriers to wholeness. The removal of these barriers is more important than the selection of the correct botanical or nutritional supplement.

Triggers are current negative influences on the child. A trigger can be subtle. Barriers are typically strong, dramatic roadblocks to health. A trigger can be a school curriculum that does not fit with a child's learning style. It can be an excessive schedule that doesn't allow enough down time, or it can be an overworked parent who is unable to provide adequate face time. Strive to identify as many of these as you can and bring pressure to move these triggers in a positive direction.

Challenges are areas of struggle for the child. These are the opposite of strengths: realms of the child's functioning that below the norm. This is an area that the child does poorly in. It can be reading skills, social skills, coordination, or even low energy. Work to identify and build supports to help the child compensate. Also, recognize that the child's world should not be focused on challenges. That is, if the child struggles with reading, make sure his or her school day has enough variety and touches on his or her strengths as well. Don't have the child spend each evening immersed in reading time, which may be a painful reminder of hardship and struggle. Balance is the key.

Finally in your treatment plan, identify the key symptom pattern that must be addressed. For the purposes of this article, the pattern will be broken down into mood issues: mild depression, moderate-to-severe depression, and bipolar-type symptoms.

Each symptom group will present with a core recommended treatment that is based upon a combination of evidence base and clinical experience. Given the lack of dose finding studies and randomized controlled trials on these supplements in the pediatric population, many of these specific dosage recommendations arise from an extrapolation of the adult data and personal clinical experience.

1. Mild depression
   - B complex 50 mg, vitamin C (1000 if ≤8 years of age, 500 mg if >8 years of age), EPA (700 mg if ≤8 years of age, 1000 mg if >8 years of age)
   - St John's wort (300 mg twice daily for if ≤8 years of age, 600 mg every day before noon and 300 mg at bedtime if >8 years of age)
   - Reduce sugar, eliminate caffeine, increase protein

   Add-ons:

Low energy:	*Rhodiola rosea* 100 to 300 mg twice daily after breakfast and at noon *Ginkgo biloba* 80 to 160 mg twice daily after breakfast and at noon
Irritability:	calcium 400 to 800 mg; magnesium 200 to 400 mg *Melissa officinalis,* not standardized (typically 1 to 2 capsules twice daily)
Sleeplessness:	Valerian (*Valeriana officinalis*), standardized to contain 0.8% valerenic acid, 250 mg, 1 twice daily or 2 at night
Poor concentration:	*Centella asiatica*, 100 mg not standardized (typically 1 to 2 capsules in the morning); *Bacopa monnieri,* 200 mg not standardized (typically 1 to 3 capsules in the morning)
Anxiety:	Inositol 2 to 4 g twice daily or 3 times daily 5-HTP 20 to 200 mg twice daily
Atypical depression:	Chromium picolinate 200 to 400 µg twice daily

2. Moderate-to-severe depression
   - B complex 50mg, vitamin C (500 mg if 8 years or under, 1000 mg if older than 8 years), EPA (700 mg if 8 years or under, 1000 mg if older than 8 years)
   - Reduce sugar, eliminate caffeine, higher protein
   - SAMe 200 to 800 mg AM/PM on empty stomach. Start with 200 mg twice daily and increase by 200 to 400 mg per week until response noted.

- Inositol 2 to 4 g twice daily or 3 times daily
- St John's wort (if SAMe fails at 30 days/1600 mg or if cost is significant issue) 600 mg AM and 300 mg PM. Double in 3 weeks if no response

Add-ons:

Low energy:	*Rhodiola rosea* 100 to 300 mg twice daily AM/noon
	Ginkgo biloba 80 to 160 mg twice daily AM/noon
Irritability:	calcium 400 to 800 mg; magnesium 200 to 500 mg
	Melissa officinalis, not standardized (typically 1 to 2 capsules twice daily)
Sleeplessness:	Valerian (*Valeriana officinalis*)
Poor concentration:	*Centella asiatica*, *Bacopa monnieri*
Anxiety:	Inositol 2 to 4 g twice daily or 3 times daily
	5-HTP 20 to 200 mg twice daily
Atypical depression:	Chromium picolinate 200 to 400 µg twice daily or DHEA 25 to 50 mg per day of if chronic medical illness is an issue

3. Bipolar symptoms (rage, extreme irritability, dysregulation, etc)
   - EMPowerplus (Truehope Nutritional Support Ltd, Raymond, Alberta, Canada) 5 capules 3 times daily (available in powder for younger kids)
   - EPA 2 g twice daily
   - Inositol 2 to 4 g twice daily or 3 times daily
   - Choline Bititrate 250 to 500 mg twice daily (if manic)
   - *Rhodiola rosea* 100 to 300 mg twice daily (if depressed); also consider light therapy if depressed
   - Avoid SAMe, St John's wort, Ginkgo, Ginseng, 5-HTP

SUMMARY

Mood disorders represent an increasingly common clinical challenge in pediatric care. The movement to an integrative approach provides many benefits. First, the emphasis is on the holistic assessment of the whole child or teen. As we embrace the ecological nature of human existence, this broad perspective enables us to see the child more comprehensively and thus to treat him or her more effectively. This allows us to grasp the barriers, triggers, strengths, and challenges for each young person.

The integrative practitioner focuses more on symptom pattern than on *DSM* diagnosis. A whole-child approach naturally de-emphasizes labels and limitations of our diagnostic system. We can fully support the self-healing capacity of the child's ecosystem as it relates to body, mind, and spirit.

The integrative practitioner actively seeks to avoid risky and unproven pharmacological interventions if possible. This more cautious and natural approach is desired by many parents who embrace the holistic-integrative philosophy. This can be thought of as a significant and growing American subculture. As culturally sensitive practitioners, it is crucial that we work with children, teens, families, and parents within their belief systems.

The last 2 decades have seen a dramatic rise in the number of children given psychiatric medications.[62,63] If current rates persist, within a generation, half of American children will be taking psychiatric medication. Many reasons for this pattern exist. Integrative practitioners can offer a variety of safe and effective alternatives for the child or teen struggling with a mood disorder. The greatest benefit comes from seeing a child fulfill his or her true potential.

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