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Hypericum for Depression

By Peter Bongiorno, ND, LAc, and Pina LoGiudice, ND, LAc

Abstract

St. John's wort (*Hypericum perforatum*) is a very well studied botanical medicine. Despite the vast body of research, controversy still surrounds its effectiveness, and research for use in pregnancy, breastfeeding women, and children is lacking. This review focuses on the latest research and supports the use of hypericum preparations in mild to moderate depression and suggests it may be a favorable alternative to pharmaceutical treatment in pregnancy, breastfeeding women, and children, with safety in all groups. In all cases, diet, lifestyle work, and psychotherapy are recommended in tandem with hypericum supplementation for optimal results. Hypericum preparations are also known to interact with and modulate the pharmacokinetics of many medications. As a result, caution is recommended for patients on medication.

Introduction

The World Health Organization predicts depression will become the second-most burdensome disease in the next decade, with the greatest burden in North America and the United Kingdom.[1] Currently, major depression accounts for 33.3% of patients in the United States,[2] and, at 160 million prescriptions annually, antidepressants are the most prescribed medication, despite the fact that recent meta-analyses show these as no better to treat mild to moderate depression (the major prescriptive reason) than placebo.[3] This is clearly an opportunity to work with natural therapies for this condition.

Hypericum oil has a history of being used topically to treat burns and hemorrhoids, to reduce inflammation, and as an anesthetic and an antiviral. Extracts of *Hypericum perforatum* are now becoming one of the standard treatment considerations for antidepressant therapy.[4]

This review outlines and summarizes a substantial body of information on hypericum for depressive illness. While studying this research and considering the potential benefits of hypericum for depression, it must be clear that the naturopathic and holistic approach should not focus merely on herbal therapy. Instead, a fully integrative plan should promote a multifactorial, individualized approach that includes diet, lifestyle changes, exercise, spiritual and psychological health, physiologic support using nutrients, and patient-specific modalities that may include homeopathy, acupuncture, massage therapy, or hydrotherapy.

Literature Review

Hypericum perforatum is a five-petal perennial flowering plant notable for its ability to treat mild to moderate depression.[5,6] Historically, hypericum was used in patients with feelings of isolation who lacked community and felt separated from the rest of the world. It has been described as a "wound healer" for nervous individuals.[7,8]

Mechanism of Action

The antidepressant mechanism of action of hypericum is not fully understood. Initially, the focus of research was on the constituent hypericin, a napthodianthrone that was believed to work as a monoamine oxidase inhibitor.[9] Hypericin and hypericin-like constituents may possibly act on acetylcholinesterase by reducing the degradation rate of acetylcholine.[10] Sedative actions come from the hypericins, bioflavones, and hyperphoria. Other reports demonstrate a serotonergic activity[11] that causes hypericum to act like a weak serotonin reuptake inhibitor (SSRI), but with fewer side effects than its pharmaceutical counterpart.[12] It is also a likely modulator of other neurotransmitter levels and receptors, including norepinephrine and dopamine, as well as γ-aminobutyric acid and glutamate amino acid neurotransmitters.[13,14,15] Hypericum may encourage production of thyroid-stimulating hormone, though a clear link has not been established.[16] Sigma 1 receptors, which are affected by antidepressant medications in animal studies, may also be affected by hypericum.[17]

One investigation examined the effect of both hypericum extract and the tricyclic antidepressant imipramine on gene transcription in the rat hypothalamus and found a significant correlation of 6 genes directly modulated by both.[18] The probability of this occurring by chance was 1.14×10^{-23}. The functions of these specific genes are varied and include cellular scaffolding and intracellular transport, protein synthesis and degradation, cellular signaling through modulation of calcium

binding proteins, and mitochondrial glycolytic energy metabolism. Although the implications of this research are not totally clear, the authors postulate that these gene functions modulated by hypericum may relate to immune and inflammatory down-regulation, as well as neuronal protection from cellular injury.

Overall, the demonstrated efficacy of this botanical in treating depression is likely due to the synergistic effects orchestrated by the components of the whole herb, working both within and peripheral to the central nervous system.

Meta-analyses of Hypericum Clinical Trials and Antidepressant Comparison Studies

The history of meta-analyzing hypericum has been full of confusion and contradiction. One meta-analysis from 1996 of 23 randomized trials included 1757 outpatients with mainly mild or moderately severe depressive symptoms. It showed that hypericum extracts were significantly superior to placebo and as effective as standard antidepressants. This analysis revealed two 0.8% dropouts for side effects with hypericum and 3.0% with standard antidepressant drugs. In this research, side effects occurred in 19.8% patients on hypericum and 52.8% patients on standard antidepressants.[19]

In contrast to this early meta-analysis, 2 well-publicized clinical studies have suggested that hypericum is ineffective in treating depression.[20] One 8-week trial employed suboptimal doses of hypericum, using 900 mg per day for patients with severe depression. If there was no response, doses were increased to 1,200 mg per day. In a previous severe depression study, patients improved significantly on hypericum, compared to placebo and the antidepressant drug imipramine, on a dose of 1,800 mg per day.[21,22] The lower-dosage study used patients with severe depression who had not responded to prior therapy. The study was criticized for several shortcomings, including failure to utilize a third arm in the study with the group receiving a standard antidepressant drug. The fact that the funding of the study was from the drug company giant Pfizer, the maker of Zoloft—the best-selling antidepressant drug at the time—also raised concerns of that the deck may have been stacked against hypericum. Still, the number reaching remission of illness was significantly higher with hypericum than with placebo, though the overall success rates were very low (14.3% for SJW; 5% for placebo).

Another 8-week study from 2002 made a similar suboptimal dosing error, and subsequently deemed hypericum to be ineffective. A valuable note in this study is that the comparison drug, sertraline (with a much stronger side-effect profile than hypericum), was still not any more effective than hypericum or the placebo.[23]

A third meta-analysis in 2008 included only trials from 1995 to 2006 that were randomized and double-blinded involving patients with major depression. Extracts of hypericum were compared with placebo or standard antidepressants, including fluoxetine, sertraline, imipramine, citalopram, paroxetine, and amitriptyline. In all, 29 studies involving 5,489 patients were analyzed in this review. Hypericum extracts tested in the trials were superior to placebo and equally as effective as standard antidepressants. Patients given hypericum extracts dropped out of trials due to adverse effects less frequently than those given older antidepressants. It concluded that the results "imply that an attempt of treating mild to moderate major depression with one of the hypericum preparations positively tested in clinical trials is clearly justified," but added that evidence is "still insufficient to draw conclusions about the efficacy of hypericum for treating severe major depression." The authors cited that the mild physical side effects associated with hypericum may be enhancing the placebo effect. A second concern was that hypericum is popular in Germany, so the more robust effects in the studies from German-speaking countries might be attributable to an "allegiance" effect. A third concern was that, although positive, the larger-scale trials used in the analysis produced overall smaller effects.[24]

Hypericum has been compared to leading antidepressant medications. In a randomized, controlled, double-blinded trial, 70 patients suffering from mild to moderate depression received 1 tablet of either hypericum extract or fluoxetine twice a day for 6 weeks. As evaluated by the 17-item Hamilton Rating Scale for Depression (HAMD), the von Zerssen depression scale (DS), and patients' response, there were significant decreases ($P<0.001$) in symptoms in the hypericum group (50%) and in the fluoxetine group (58%) on their HAMD score. The hypericum extract achieved 83% of the efficacy of fluoxetine on the HAMD and 78% on the DS. Assessments by physicians and patients indicated considerable improvement with no between-treatment differences.[25] The authors concluded that the hypericum tested in this study was therapeutically equivalent to fluoxetine and that it is a reasonable alternative to synthetic antidepressants.

Hypericum extract has similarly been tested and proven at least as effective as sertraline in the treatment of mild to moderate depression in a small group of outpatients.[26] Efficacy and tolerability of hypericum extract was also compared with imipramine and was found equivalent to the drug in treating mild to moderate depression. In addition, as expected, patients tolerated the hypericum better.[27] Overall, the literature supports the use of hypericum extract for patients with mild to moderate depression. At this point, results are not clear that there is any benefit in major depression.

Hypericum in Pregnancy

Despite considerable scientific investigation, relatively little information has been garnered regarding the use of hypericum for depression during pregnancy. A few animal studies have investigated its effect on pregnancy and progeny. A study in rats using doses up to 25 times the equivalent recommended human dose throughout gestation was unable to show any neurobehavioral or developmental effects on the offspring. Maternal weight gain or length of gestation, likewise, was not affected.[28] Other murine studies showed no significant impact on cognition or behavioral tasks. In these studies, the doses used were equivalent to human therapeutic doses, based on body surface area, and were shown to affect behaviors typically evaluated when assessing for antidepressant effects.[29,30] A final mouse study also revealed

no increased risk for structural anomalies; appropriate pup head circumference and body length were observed in both the exposed and unexposed groups. Treatment group male offspring were slightly lower in birth weight than the unexposed controls. This difference was no longer evident by postnatal day 3. These animal studies suggest a lack of structural or functional deficits attributable to hypericum exposure during gestation.[31]

Although the animal data suggests safety, human trial data is insufficient because no large clinical trials have assessed this. The information available does suggest that there is no risk to fetal development. In 1998, there were reports on 2 women who took hypericum in their pregnancies to avoid the use of conventional synthetic medications. Both cases seemed to reveal no concerns. One of these cases was of a 38-year-old woman who started hypericum at 24 weeks gestation. The pregnancy was unremarkable, with the exception of late onset of thrombocytopenia, which the author did not attribute to hypericum. The offspring was born healthy, had a normal birth weight, normal APGAR scores, and physical examination and laboratory results were normal. Infant behavioral assessment at 4 and 23 days was normal.[32] One 2006 review looked at the evidence on the use, safety, and pharmacology of hypericum. This review searched 7 databases including the Cochrane databases, MedLine, Natural Database, and Natural Standard. Some unpublished research and bibliographies were also included. Data were compiled according to grade of evidence. The researchers found varying levels of scientific evidence. They concluded that there is evidence from animal studies that hypericum during pregnancy does not affect cognitive development nor cause long-term behavioral defects, but found some evidence of lower offspring birth weight. It is important to remember that rodents have very different detoxification abilities, and extrapolation to humans may not be prudent. This review also pointed to weak scientific evidence that hypericum induces CYP450 enzymes, which may lower serum medication levels below therapeutic range—which would be of concern when administering medications during pregnancy. The authors concluded that caution is warranted with the use of hypericum during pregnancy until further high-quality human research is conducted to determine its safety.[33]

The first study of hypericum that aimed to determine whether exposure could be associated with major malformations prospectively followed 54 pregnant women using hypericum (average daily dose among those taking tablets was 615 mg; doses could not be estimated in 3 subjects taking teas, 1 subject taking tincture, and 1 subject taking granules) and compared them to a matched group of 54 pregnant women taking other pharmacologic therapy for depression, and a third group of 54 healthy pregnant women. In this prospective study, in these 54 patients the average daily dose was 615mg among those using tablets of extracts. The study showed that malformation rates were similar across the 3 groups, with 5% in the hypericum group, 4% in the pharmaceutical group, and 0% in the healthy group (P=0.26). This was not different than the 3% to 5% risk expected in the general population. Live birth and prematurity rates were also not different among the 3 groups. The authors suggested that this first study on the effects of hypericum in human pregnancy provides some evidence of fetal safety.[34] Further studies are needed to establish the definitive safety of hypericum extracts in pregnancy.

Hypericum in Breastfeeding

The non-breastfeeding postpartum depression patient certainly has a vast array of natural choices for healing at her disposal. The situation is a bit more complicated in women who are currently breastfeeding, due to a relative dearth of information on the safety of natural remedies for the breastfeeding baby.

Studies using hypericum during breastfeeding are starting to support the use and safety for depressed mood in mothers while breastfeeding. Animal studies using doses up to 25 times the equivalent recommended human dose throughout lactation were unable to show any neurobehavioral or developmental effects on offspring.[35]

Human studies are beginning support the use of hypericum in breastfeeding women. In 1 small, prospective, observational cohort study, 33 nursing mothers using hypericum (Group 1) were compared with 101 disease-matched (Group 2) and 33 age- and parity-matched healthy controls (Group 3). Information collected included maternal and neonatal demographics, breastfeeding duration, usage of hypericum, maternal and infant adverse events, infant weight over the first year of life, and ability to produce breast milk. The evaluation found no significant difference in the frequency of maternal report of decreased milk production or in infant weight over the first year of life. Whereas only 1 infant each in Groups 2 and 3 was reported to be colicky, 2 cases of "colic," 2 of "drowsiness," and 1 of "lethargy" were reported in Group 1 (P <0.01; Group 1 vs. Group 2, P<0.01; Group 1 vs. Group 3, P=0.20). Although 3 of these women in Group 1 consulted their doctors, specific medical treatment was not required.[36]

A review mentioned earlier for pregnancy published in 2006 also surveyed evidence on the use, safety, and pharmacology of hypericum focusing on issues pertaining to pregnancy and lactation. Culling 7 databases (see above) the researchers found varying levels of scientific reliability with evidence of some side effects during lactation. Strong scientific evidence (see above cohort) confirmed that hypericum consumption during lactation did not affect maternal milk production or infant weight, but may cause colic, drowsiness, or lethargy. The authors concluded that hypericum use during lactation appears to be of minimal risk, but could cause some side effects.[37]

A 2006 report of 5 mothers who were taking 300 mg of St. John's wort 3 times daily and their breastfed infants were evaluated. In this study, 36 milk samples of foremilk and hindmilk, as well as plasma samples from 5 mothers and 2 infants, were collected during an 18-hour period. These were analyzed for hyperforin levels by tandem mass spectrometry. The researchers found that hyperforin is excreted into breast milk at low levels, with hyperforin levels at the limit of quantification in the plasma samples

of 2 infants. Results indicate that infant exposure to hyperforin through milk is comparable to levels of medication reported in most studies assessing antidepressants or neuroleptics. No side effects were seen in the mothers or infants. Authors noted that this work adds to the evidence of the relative safety of hypericum while breastfeeding.[38] Since adult exposure to hypericum reveals a more minimal side effect profile than antidepressant medications, it may be possible that babies receiving breast milk may also have fewer side effects than they would with conventional medication use. Of course, the detoxification systems of children are not as robust as in the adult, so more studies would be needed to confirm this postulation before considering hypericum as a standard treatment in breastfeeding mothers.

Hypericum in Children

Three open-label evaluations of children and adolescents with depression have been conducted. The first investigation surveyed 101 children under 12 years of age who were treated for a minimum of 4 weeks with an extension to 6 weeks with parental consent and medical practitioner recommendation. The dosage used ranged from 300 to 1,800 mg per day (1 coated tablet containing 300 mg hypericum extract, which was standardized to contain 900 µg hypericin). Compliance, tolerability, and efficacy were assessed every 2 weeks by both physicians and parents. Based on the data available for analysis, the number of physicians rating effectiveness as good or excellent was 72% after 2 weeks, 97% after 4 weeks, and 100% after 6 weeks (with the final evaluation including only 76% of the initial sample). Parental ratings corroborated physician assessments. The children had no reported side effects. The results of this study suggest that hypericum is a potentially safe and effective treatment for children with symptoms of depression.[39]

The second study was an 8-week, prospective, open-label, outpatient study in the treatment of youth diagnosed with major depressive disorder. The study included 33 youths aged 6 to 16 years (mean age of 10.5) who met DSM-IV criteria for major depressive disorder of at least moderate severity. Patients were initially prescribed 150 mg hypericum extract 3 times daily. If a patient did not meet the response criteria at the end of week 4, the dose was increased to 300 mg 3 times daily. After 4 weeks of hypericum therapy, 22 youths had their dose increased to 900 mg/day. Twenty-five of the patients (approximately 80%) met response criteria after 8 weeks of treatment. Response rates were based on a Children's Depression rating scale score of less than or equal to 28, Clinical Global Impressions scale of less than 2. Additionally, subjects and their families were asked whether or not they wished to continue taking hypericum at the end of study participation. Overall, hypericum was well tolerated. Of the patients who completed 8 weeks, 93% chose to continue their treatment with hypericum after their participation in the study ended. The most common side effects were generally mild and transient and included dizziness, increased appetite, and loose stools. No clinically significant changes in weight, vital signs, laboratory parameters, or electrocardiogram were noted.[40]

The most recent study was an 8-week open-label study of 26 adolescents (12 to 17 years old) diagnosed with major depressive disorder who were given hypericum 300 mg 3 times daily. Of the 11 patients who completed the study, 9 (82%) showed significant clinical improvement at week 8. Statistically significant clinical improvements appeared during the first week and continued to be noted until week 8. Mild and transient side effects were noted and included restlessness, dry mouth, nightmares, confusion, loss of attentiveness, nausea, and fatigue. There were no significant changes in blood tests, urinalysis, weight, blood pressure, or electrocardiogram. Also of note, 15 patients withdrew from the study due to persisting or worsening depression or noncompliance.[41] In the above 3 studies, side effects were minimal. When side effects occurred that were considered to be possibly related to hypericum, these generally were short-lived and mild symptoms. The most common side effects reported were dizziness, increased appetite, constipation, or loose stools.[42]

Hypericum Dosage

In 1 review of more than 3,000 depressed patients spanning 34 double-blinded controlled trials, the effective dosage level of hypericum for mild to moderate depression was found to range between 500 and 1,000 mg of standardized alcohol extract per day.[43] For patients with pre-existing conductive heart dysfunction or elderly patients, high-dose hypericum extract has found to be safer with regard to cardiac function than tricyclic antidepressants[44] and may be considered as a first-line therapy for cardiac patients with depression. The most commonly recommended amount of hypericum is 300 mg of standardized extract 3 times per day for mild to moderate depression. Doses as high as 1,800 mg per day have been used for moderate to severe depression.[45] Common tincture dose ranges have been suggested at 3–6 mL per day of a 1:5 tincture[46] and 2–6 mL for a 1:2 liquid extract.[47] For children, typical doses studied are 300–900 mg per day, although one study did use 1,800 mg per day.[48]

Hypericum Interactions

Although now not considered a concern regarding interaction with monoamine oxidase (MAO)–inhibiting drugs or tyramine containing foods, hypericum has been shown to have the ability to either enhance or reduce the circulating levels of certain drugs.[49,50,51,52] Hypericum is known to induce enzymes of the cytochrome P450 system (3A4 and 1A2) as well as P-glycoprotein from the intestinal wall. Hypericum interacts with and lowers the effectiveness of oral contraceptives. Three studies indicate an alteration of the pharmacokinetics of the oral contraceptive with coadministration of hypericum.[53,54,55] Two other studies report breakthrough bleeding and spotting.[56,57]

Hyperforin, a constituent of hypericum, induces metabolic activity of cytochrome P450 2C19 and cytochrome P450 3A4 in the liver.[58] A study using the platelet inhibitor clopidogrel found that 2 out of 10 patients using clopidogrel are poor responders, but in these patients 300 mg of hypericum for 2 weeks resulted in an increase of platelet inhibition of 20%. A previous study

using 300 mg 3 times per day resulted in an increase of 36%. Furthermore, no negative change in low-density lipoproteins was seen in patients on statin medications.[59] Hypericum may be a good choice in poor responders, or to help lower the dose necessary in normal responders who are having side effects.

If a patient is taking specific or multiple medications, hypericum should be used with caution or avoided altogether, and other options should be considered. See Figures 1 and 2 for more specific information.

Figure 1
Medications Known to Interact with Hypericum

Alprazolam
Amitriptyline
Cyclosporine
Digoxin
Indinavir
Irinotecan
Methadone
Nevirapine
Oral contraceptives
Phenprocoumon
Simvastatin
Tacrolimus
Theophylline
Topo II-poisoning chemotherapy regimens
Verapamil
Warfarin

Hypericum Toxicity

The side-effect profile of hypericum extract is minor, especially when compared to the well-known side effects of antidepressant medications.[62] Symptoms matching excessive levels of serotonin should also be monitored when using hypericum with SSRIs, tryptophan, or 5-hydroxytryphan. According to the U.S. Food and Drug Administration, symptoms of "serotonin syndrome" may include mental status changes (e.g., agitation, hallucinations, coma); autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia); neuromuscular aberrations (e.g., hyperreflexia, incoordination); and/or gastrointestinal tract symptoms (e.g., nausea, vomiting, diarrhea). Severe cases can resemble neuroleptic malignant syndrome (NMS), which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. An example of this was reported in a study of 4 elderly patients who ostensibly developed serotonin syndrome as a result of an interaction between tramadol and mirtazapine.[63] Although polypharmacy of antidepressants has caused this syndrome, no reports of natural substances causing this syndrome have been reported to date. Since its action on serotonin is minor, it is unlikely that hypericum would cause this syndrome, but monitoring is prudent.

Although hypericum has been demonstrated to induce photosensitivity in some patients (less than 1% of people taking 900 mg per day or more), this is not likely with standard dosages. Cases of photosensitivity have occurred mainly in HIV patients using larger than normal quantities for an antiviral effect.[64] It has been suggested that tincture or extract can be substituted for capsules if photosensitivity occurs.[65]

Figure 2
Known Interactions of Hypericum[60,61]

Agents Whose Blood Concentrations Are Decreased by Hypericum	Conditions That May Be Caused by Hypericum	Agents Whose Pharmacokinetics Are Not Altered by Hypericum	Agent Whose Efficacy is Enhanced by Hypericum
Anticancer drugs: irinotecan and its active metabolite SN-38 *Anticoagulants:* phenprocoumon and warfarin *Antidepressants:* amitriptyline *Anti-HIV agents:* protease inhibitor indinavir Reverse transcriptase inhibitor nevirapine *Antihistamines:* fexofenadine *Bronchodilators:* theophylline *Cardiovascular drugs:* digoxin and simvastatin *Immune suppressants:* cyclosporine and tacrolimus *Opiates:* methadone *Sedatives:* midazolam	Serotonin syndrome when coadministered with selective serotonin-reuptake inhibitors (e.g., sertraline, paroxetine) Break-through bleeding and unplanned pregnancies when used concomitantly with oral contraceptives Hypoglycemia when used concomitantly with tolbutamide	*Anticonvulsants:* carbamazepine *Cardiovascular drugs:* pravastatin *Cough medication:* dextromethorphan *Immunosuppressants:* mycophenolic acid	Clopidogrel

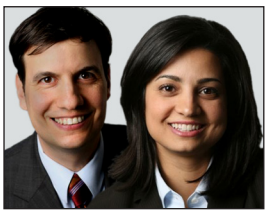
Figure 3
Summary

Latin Name (Common Name)	Dosage	Toxicity/ Interactions	Usage Notes
Hypericum perforatum (St. John's wort)	300 mg of standardized extract t.i.d., up to 600 mg t.i.d. in adults; 300 mg to 900 mg q.d. in children	- Minimal side effect profile - Avoid with birth control pills - Possible photosensitivity in certain populations - Serotonin syndrome theoretically possible when combined with SSRIs or tryptophan supplementation - Known interactions with pharmaceuticals by changing medication availability by affecting P450 enzyme	- Helpful for both depressed mood and depression with anxiety - May be indicated as a first-line therapy for cardiac patients with depression - Some studies in children, pregnant and breastfeeding mothers show effectiveness and absence of side effects

Conclusion

Depression is an increasing concern with substantial increases in incidence forecasted for the next 10 years. Natural medicine modalities should include dietary, lifestyle, and psychologic treatments. The vast body of research, as well as historical use, suggests that hypericum is a useful ally as part of a broader treatment plan for adults with minor to moderate depression. Emergent studies suggest that hypericum may be helpful and does not cause any birth defects, may be useful in adolescents with depression, and has a favorable side effect profile. However, hypericum is known to have interactions and modulate the pharmacokinetics of many medications. As a result, caution is recommended with patients on medication(s). Although more research is necessary to establish its definitive safety in pregnancy and lactation, hypericum may represent a lesser risk to the developing child when compared to pharmaceutical alternatives in women whose depression is not controlled by lifestyle and diet.

About the Authors



Peter Bongiorno, ND, LAc, and Pina LoGiudice, ND, LAc, codirect InnerSource Natural Health and Acupuncture, with practices in New York City and Huntington (Long Island), New York. Bongiorno focuses on adult chronic disease and LoGiudice cares for patients with fertility, pregnancy, and pediatric concerns. Before graduating naturopathic medical school and completing their masters work in acupuncture at Bastyr University, they both completed predoctoral work in the department of Clinical Neuroendocrinology at the National Institutes of Mental Health, part of the National Institutes of Health in Bethesda, Md. Bongiorno is a major contributor to the 3rd edition of the *Textbook of Natural Medicine,* and he has recently authored the textbook *Healing Depression: Integrated Natural and Conventional Therapies* (CCNM Press, 2010). LoGiudice contributed to the chapters on pregnancy, breastfeeding, and children. Their website www.innersourcehealth.com.

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