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## Review

## Second-tier natural antidepressants: Review and critique

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## ABSTRACT

The use of Complementary and Alternative Medicine (CAM) for physical and mental problems has increased significantly in the US over the past two decades, and depression is one of the leading indications for the use of CAM. This article reviews some of the lesser-known natural products with potential psychiatric applications that are starting to emerge with some scientific and clinical evidence and may constitute a next wave of natural antidepressants: *Rhodiola rosea*, chromium, 5-Hydroxytryptophan (5-HTP) and inositol. Background information, efficacy data, proposed mechanisms of action, recommended doses, side effects, and precautions are reviewed. We found some encouraging data for the use of these natural products in specific populations of depressed patients. *R. rosea* is an adaptogen plant that can be especially helpful in treating asthenic or lethargic depression, and may be combined with conventional antidepressants to alleviate some of their common side effects. Chromium has a beneficial effect on eating-related atypical symptoms of depression, and may be a valuable agent in treating atypical depression and seasonal affective disorder. Inositol may be useful in the treatment of bipolar depression when combined with mood stabilizers. Evidence for the clinical efficacy of 5-HTP is also promising but still preliminary. Although more well-designed and larger controlled studies are needed before any substantive conclusions can be drawn, the available evidence is compelling and these natural products deserve further investigation as a possibly significant addition to the antidepressant armamentarium.

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## 1. Introduction

In the last decade there has been a significant increase in the use of Complementary and Alternative Medicine (CAM) for physical and mental health problems in the US and worldwide. The 2007 National Health Interview Survey (NHIS) reported that 38% of US adults and approximately 12% of children had used some form of CAM in the past 12 months, especially natural products. Depression, anxiety, and insomnia are among the most common reasons for people to use complementary therapies (Kessler et al., 2001), and persons with major depressive disorder (MDD) may be more likely to use CAM therapies than those without it (Unützer et al., 2000). Many patients self-treat their mood disorder with CAM without professional supervision, and often without disclosing it to their psychiatrist or primary physician (Elkins et al., 2005). Moreover, most patients who use CAM remedies also take prescription antidepressants concurrently, risking potentially dangerous adverse herb/drug interactions. While most natural psychotropics are generally considered safe, they are not necessarily risk free, and the common public misconception that natural equals safe has been belied by various reports of toxic reactions from these agents, which may be due to intrinsic toxicity, contamination, or interaction with other drugs.

Although a multitude of natural medications are available for the treatment of mood disorders, the evidence for their effectiveness remains limited for most, if not demonstrated at all for many. According to Astin et al. (1998), the five most widely used CAM approaches are acupuncture, chiropractic, homeopathy, herbal medicine, and massage. A few natural psychotropics have been more extensively examined in reasonably well-designed, placebo-controlled, double-blind studies, and in systematic reviews and meta-analyses. Well-studied products include St John's Wort, S-adenosyl-L-methionine (SAME) and Omega-3 fatty acids (Mischoulon, 2009), for which there is a growing consensus of antidepressant effectiveness and safety. Other alternative therapies that are also gaining acceptability as potential antidepressants include folate (Fava and Mischoulon, 2009), acupuncture (Smith et al., 2010) and exercise (Freeman, 2009; Greer and Trivedi, 2009).

There are also other products that are emerging with early scientific and clinical evidence for effects on mood and may deserve evaluation as a next wave of potential natural antidepressants, both as monotherapy and as adjuncts to well established treatments. This article will review four of these second-tier natural products for mood disorders: *Rhodiola rosea*, Chromium, 5-Hydroxytryptophan and Inositol.

## 2. Methods

A Pubmed/Medline literature search was performed, using the search terms *Complementary Medicine, Complementary Therapy, Alternative Medicine, Alternative Therapy, Depression, Depressive Disorder, R. rosea, Chromium, 5-Hydroxytryptophan* and *Inositol*. We included systematic reviews, meta-analyses, RCTs, case control studies, open studies, case series, and case studies for each therapy. We obtained the original articles where possible, and also hand-searched for cross-referenced articles and books. Searches were restricted to English language publications. Restrictions on year of publication were not applied.

### 3. *R. rosea*

*R. rosea* is a popular plant widely distributed at high altitudes in the mountainous regions of Europe and Asia, where it is also known as “golden root” or “arctic root”. The roots of the plant have been used for centuries in the traditional medicine of Asia, Scandinavia, and Eastern Europe as a health-enhancing supplement for stimulating the nervous system, enhancing physical and mental performance, alleviating fatigue, psychological stress, depression, impotence, and preventing high altitude sickness. *R. rosea* has been classified by Russian researchers as an adaptogen, a substance that nonspecifically increases the resistance of an organism to a variety of chemical, biological, and physical stressors.

#### 3.1. Mechanisms of action

*R. rosea* contains many biologically active substances including flavonoids, monoterpenes, triterpenes, phenolic acids, phenylethanol derivatives (salidroside and p-tyrosol) and phenylpropanoid glycosides such as rosin, rosavin, and rosarin, comprehensively referred to as rosavins and specific to this plant. The stimulating and adaptogenic properties of *R. rosea* are attributed specifically to p-tyrosol, salidroside, rosavins, and additional phenolic compounds, while the high content in organic acids and flavonoids contributes to the strong antioxidant properties of the plant (Ming et al., 2005). According to the revised 1989 Soviet Pharmacopeia, *R. rosea* extracts are standardized for both rosavins and salidroside. The extracts used in most human clinical studies are standardized to minimum 3% rosavins and 0.8% salidroside, because the naturally occurring ratio of these compounds in *R. rosea* root is approximately 3:1.

The adaptogenic properties and central nervous system activities of *R. rosea* have been attributed primarily to its ability to influence levels and activity of biogenic monoamines such as serotonin, dopamine, and norepinephrine in the CNS (Kelly, 2001). It is believed that the changes in monoamine levels are due to *R. rosea*'s inhibition of the activity of enzymes responsible for monoamine degradation (monoamine oxidase and catechol-O-methyltransferase) and to facilitation of neurotransmitter transport within the brain. *R. rosea* could therefore be said to function as an enhancer of the catecholaminergic system. A recent study demonstrated that *R. rosea* root extracts have a potent inhibitory activity on MAO-A and MAO-B, greater than 80% at a concentration of 100 µg/ml (Van Diermen et al., 2009). This might primarily account for the extract's antidepressant activity and suggests applications in other CNS disorders such as Parkinson's and Alzheimer's disease. Recent animal studies have also demonstrated that *R. rosea* may enhance the level of 5-hydroxytryptamine and promote the proliferation and differentiation of neural stem cells in the hippocampus of rats with depression induced by chronic mild stress, and may protect injured hippocampal neurons (Qin et al., 2008).

*R. rosea* may exert activity on the opioid system, by induction of opioid peptide biosynthesis and through the activation of central and peripheral opioid receptors (Lishmanov et al., 1987; 1997). Moreover, *R. rosea*'s activity in the opioid system is involved in its anti-stress effect. Animal models demonstrated that *R. rosea* modestly increases serum beta-endorphins that protect against subsequent stress-induced excess endorphin elevation, and moderates the release of opioid peptides that occurs as part of the pituitary–adrenal axis response to stress. This dampened release protects against sudden excess opioid and catecholamine levels, while allowing a more moderate release that increases stress tolerance without damaging the CNS or the cardiovascular system (Lishmanov et al., 1987; Maslova et al., 1994).

It has also been reported that *R. rosea* can reduce the secretion of corticotrophin-releasing factor (CRF), the major physiological mediator of stress (Lishmanov et al., 1987; Maslova et al., 1994), and may reverse the anxiogenic activity of CRF (Mattioli and Perfumi, 2007a,b).

### 3.2. Efficacy

Although *R. rosea* has been intensively studied in Russia and Scandinavia for more than 40 years, most of this research is unavailable for review and verification because it is published in Slavic and Scandinavian languages and has yet to be translated to English. Only in the last decade has the plant started to gain popularity in Western Europe and the US and to become the focus of systematic research. The available literature generally supports its adaptogenic properties. *R. rosea* has been shown to offer generalized resistance against physical, chemical and biological stressors and to elicit antidepressant activity both in animals and humans, and has been proposed as a remedy for asthenic or lethargic conditions (characterized by decline in work performance, sleep disturbances, poor appetite, irritability, hypertension, headaches, and fatigue) secondary to intense physical or intellectual strain (Brown et al., 2002).

Two recent randomized, double-blind, placebo-controlled trials of the standardized extract of *R. rosea* root (SHR-5)

provide a degree of support for the beneficial effects of SHR-5 on healthy subjects under stressful conditions. The first study assessed fatigue and mental performance (associative thinking, short-term memory, concentration, speed of audio-visual perceptions, and other parameters defined as "Fatigue Index") in a group of 56 young, healthy physicians on night duty receiving a low-dose treatment of SHR-5 (170 mg/day). The tests were performed before and after the night duty during three two-week periods in a double-blind cross-over trial. A statistically significant improvement in fatigue and mental performance was observed in the treatment group during the first 2 weeks. By 6 weeks, however, the effect appeared to be lost, possibly due to a short-term benefit of SHR-5, or to the low dose used, or the cross-over design of the study (Darbinyan et al., 2000).

In the second study, 40 medical students were randomized to receive either a low dose of SHR-5 (100 mg/day) or placebo for 20 days during a stressful examination period. Subjects receiving *R. rosea* demonstrated significant improvements in physical fitness, mental fatigue, psychomotor performance and general well-being. They also reported improvement in sleep patterns, reduced need for sleep, greater mood stability, and a greater motivation to study (Spasov et al., 2000).

A recent double-blind, placebo-controlled study found that *R. rosea* extract exerted an antifatigue effect that increases mental performance, particularly the ability to concentrate, and decreases cortisol response to awakening stress in patients with stress-related fatigue. The study was conducted on 60 patients, at a dose of 576 mg/day, with assessments on day 1 and after 28 days of medication (Olsson et al., 2009).

Significant improvement in physical and cognitive deficiencies was observed in a 12-week monitoring study in which a *R. rosea* extract was given in combination with vitamins and minerals in 120 adults (83 women, 37 men, ages 50–89 years old), at two different dosages. The symptoms evaluated were physical disturbances such as exhaustion, decreased motivation, daytime sleepiness, decreased libido, sleep disturbances, and cognitive complaints such as concentration deficiencies, forgetfulness, decreased memory, susceptibility to stress, and irritability (Fintelmann and Gruenwald, 2007).

Few studies thus far have explored the antidepressant effect of *R. rosea*. Studies on animal models of depression are consistent in reporting its antidepressant-like effect (Mattioli and Perfumi, 2007a,b; Chen et al., 2009; Panossian et al., 2008). Previous studies have shown that when an extract of *R. rosea* was combined with tricyclic antidepressants there was a marked reduction in antidepressant side effects and an amelioration of psychopathological symptoms in depressed patients (Brichenko et al., 1986; Brichenko and Skorokhodova, 1987).

There is only one study investigating the antidepressant effect of *R. rosea* monotherapy in depressed patients. Darbinyan et al. (2007) conducted a 6 week double-blind, placebo-controlled, randomized pilot study with 89 patients with mild to moderate depression. Patients were randomized to receive placebo or SHR-5 at two different doses (340 or 680 mg/day). The efficacy of SHR-5 was assessed on the basis of total and specific subgroup scores of the Hamilton Rating Scale for Depression (HAM-D). Patients who received SHR-5 reported a statistically significant reduction of depressive symptoms at

both doses, while patients on placebo did not show significant improvement. No side effects were reported (Darbinyan et al., 2007).

There is also a single pilot study investigating the efficacy of *R. rosea* in the treatment of anxiety in 10 patients with Generalized Anxiety Disorder (GAD). Patients received a total daily dose of 340 mg of *R. rosea* extract for 10 weeks. They reported a significant reduction in the Hamilton Anxiety Rating Scale (HARS) scores at the end of the study. Half of the participants had at least a 50% decrease on the HARS and were considered responders. Four patients (40%) achieved a HARS score of  $\leq 8$ , meeting criteria for remission (Bystritsky et al., 2008). The study is limited by the small sample size, the fixed dosing schedule, and the open-label design, which does not allow for control of placebo effects. Open-label studies with herbal remedies frequently produce high response rates that are not always confirmed in subsequent controlled clinical trials (see Table 1 for summary of selected trials).

### 3.3. Safety and tolerability

*R. rosea* appears to have an excellent safety profile. Side effects are uncommon and mild, and can include allergy, irritability, insomnia, fatigue, and unpleasant sensations, especially at high doses. An increase in irritability and insomnia within several days has been reported in some individuals at doses of 1.5–2.0 g of *R. rosea* extract standardized for 2% rosavin. The extract is best absorbed when taken on an empty stomach 30 min before meals, and should be taken early in the day because it can interfere with sleep or cause vivid dreams. When side effects occur, a smaller dose with very gradual increases can be suggested.

*R. rosea* does not appear to interact with other medications such as warfarin and theophylline, and can be of value in patients who take multiple drugs (Panossian et al., 2009). This is particularly significant in light of the increasing numbers of adverse drug–drug interactions that have been described for various herbal products. For example, St. John's Wort has demonstrated Cytochrome P450-related interac-

tions with several drugs including warfarin, theophylline, cyclosporine, digoxin, anti-HIV drugs and oral contraceptives (Mischoulon, 2007). We found no data concerning efficacy, safety and pharmacological interaction of *R. rosea* used in combination with SSRIs or SNRIs. However, the concomitant use of *R. rosea* and tricyclic antidepressants has been reported to have favorable effect in terms of both antidepressant efficacy and reduction of side effects (Brichenko et al., 1986; Brichenko and Skorokhodova, 1987).

Evidence for the safety and appropriateness of *R. rosea* supplementation during pregnancy and lactation is currently unavailable, and *R. rosea* is therefore not recommended for pregnant women or during breastfeeding. Finally, *R. rosea* has not been studied in bipolar depression, and should be used with caution in patients with bipolar spectrum disorders because of its activating effect, which could present a risk of cycling.

### 3.4. Recommendations

*R. rosea* has a long history as a valuable medicinal plant with high versatility in preventing and alleviating a wide range of medical conditions, including depression and anxiety. Unfortunately, the majority of research publications are unavailable for review and this hinders careful scrutiny of the traditional claims of antidepressant and CNS-enhancing properties. As mentioned earlier, the clearest indication for administration of *R. rosea* appears to be for asthenic conditions. The adaptogenic activity, in combination with monoamine modulation, suggests a promising application in the treatment of depression, and the available studies on animals and humans have provided encouraging evidence of its antidepressant activity.

More controlled studies are warranted to explore the curative benefits of *R. rosea* and its use as antidepressant monotherapy or augmentation. The concomitant use of *R. rosea* with SSRIs and SNRIs might be especially helpful for common antidepressant side effects such as poor memory, sexual dysfunction and weight gain. Considering the favorable side-effect profile, along with the popularity of herbal remedies in

**Table 1**  
Selected clinical trials of *Rhodiola rosea*.

Authors (year)	Treatment	Study design	Study length	Sample size and characteristics	Outcome measures/results
Bystritsky et al. (2008)	SHR-5 (340 mg/day)	Open-label	10 weeks	N = 10, with GAD	Significant reduction in the HARS. 5/10 responded and 4/10 achieved remission (HARS $\leq 8$ )
Darbinyan et al. (2000)	SHR-5 (170 mg/day) vs placebo	Double-blind, randomized, placebo-controlled, cross-over	3 two-week periods	N = 56, young healthy physicians on night duty	Significant improvement in the "Fatigue Index" in the SHR-5 group during the first 2 weeks
Darbinyan et al. (2007)	SHR-5 (340 or 680 mg/day) vs placebo	Double-blind, randomized, placebo-controlled	6 weeks	N = 89, with mild to moderate depression	Significant improvement in HAM-D in the SHR-5 groups at both doses
Fintelmann and Gruenwald (2007)	SHR-5 plus vitamins and minerals (150 or 300 mg/day)	Monitoring study	12 weeks	N = 120, age 50–89 years old	Significant improvement in physical and cognitive deficiencies. Global assessment of efficacy rated "good" or "very good" in 81% of patients
Olsson et al. (2009)	SHR-5 (576 mg/day) vs placebo	Double-blind, randomized, placebo-controlled	4 weeks	N = 60, with stress-related fatigue	Improvement in fatigue, concentration, and decreased cortisol response to awakening stress in the SHR-5 group
Spasov et al. (2000)	SHR-5 (100 mg/day) vs placebo	Double-blind, randomized, placebo-controlled	20 days	N = 40, medical students	Significant improvement in physical and mental performance, general well-being, mood stability, motivation, and sleep in the SHR-5 group

SHR-5: standardized extract of *R. rosea* root; GAD: generalized anxiety disorder; HAM-D: Hamilton Rating Scale for Depression; HARS: Hamilton Anxiety Rating Scale; NS: non significant.

our culture, *R. rosea* deserves further study in the treatment of depression as well as anxiety.

#### 4. Chromium

Chromium is a widely used nutritional supplement marketed for a wide range of applications. Estimated sales of chromium supplements in U.S. amounted to \$85 million in 2002, representing 5.6% of the total mineral-supplement market (Nutrition Business Journal, 2003). Chromium is sold as a single-ingredient supplement as well as in combination formulas, particularly those marketed for weight loss and performance enhancement.

Among the nine natural oxidation states of chromium, the hexavalent form is highly toxic (carcinogenic, allergic, and associated with the development of asthma, cardiovascular and renal disorders), but trivalent chromium is an essential microelement of living organisms, involved in the metabolism of carbohydrates, proteins and lipids. It acts by increasing the efficiency of insulin action and utilization, and plays a major role in cellular insulin sensitivity and insulin-regulating activities (Anderson et al., 1997a,b; Cefalu et al., 2002). Chromium deficiency has been implicated as one of the causes of diabetes mellitus (Hummel et al., 2007), and its supplementation improves glucose tolerance in diabetic patients (Abdourahman and Edwards, 2008).

Recent clinical and experimental studies have also reported antidepressant activity of chromium in affective disorders and particularly in atypical depression, characterized by increased appetite, hyperphagia, and carbohydrate craving, among other clinical features. The possible use of a compound such as chromium that exerts a normalizing effect on insulin sensitivity and appetite while having antidepressant activity may therefore be a promising therapeutic option in patients with atypical depression, a subtype of depression typically associated with overeating and weight gain.

##### 4.1. Mechanisms of action

The mechanism of the proposed antidepressant effect of chromium is not entirely understood. It is difficult to test whether deficiencies in dietary chromium produce depressive symptoms, as there are currently no reliable analytical methods to determine the nutritional chromium status of patients (Mertz, 1993). Furthermore, chromium deficiency in patients receiving total parenteral nutrition results in gross disorientation and a syndrome similar to hepatic encephalopathy, but chronic depression has not been observed (Nielso, 1994).

One potential mechanism for the antidepressant activity of chromium may involve an enhancement of monoaminergic neurotransmission. By enhancing insulin sensitivity, chromium may increase insulin-mediated transport of the serotonin precursor tryptophan across the blood–brain barrier into the CNS, thus increasing serotonin synthesis and function (Fernstrom, 1976; McCarthy, 1994). This could account for the very rapid changes in mood and other symptoms observed in depressed patients receiving chromium supplementation. Moreover, chromium can induce and enhance norepinephrine release (Liu and Lin, 1997), which could also contribute to an antidepressant effect.

Recent neuroendocrine studies have shown that administration of chromium decreases functional activity of serotonin 5-HT 2A receptors in animals and humans (Attenburrow et al., 2002; Khanam and Pillai, 2006). The mechanism of this effect is not clear, and may involve changes in receptor expression, signal transduction, or intracellular messengers. Since reduction in 5-HT 2A receptor sensitivity also occurs following chronic treatment with certain antidepressant drugs (Maj et al., 1996), the 5-HT2A receptor downregulation induced by chromium might be related to its antidepressant effect. Moreover, chromium administration in rats produces a significant increase in plasma and brain tryptophan and brain 5-HT content (Attenburrow et al., 2002). The authors did not find the same effect in humans, perhaps due to the substantially lower doses and shorter duration of treatment used in human volunteers compared to rats.

Finally, a recent experimental study has implicated the involvement of the glutaminergic system via the N-methyl-D-aspartate (NMDA) and the alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors in the antidepressant activity of chromium (Piotrowska et al., 2008).

##### 4.2. Efficacy

The use of chromium in depression was first reported in 1999 by McLeod et al. Five patients with treatment refractory dysthymia achieved full remission after adding chromium picolinate (400 µg daily) to their antidepressant regimen (sertraline or nortriptyline). Single-blind substitution of chromium with other dietary supplements demonstrated specificity of response to chromium supplementation in all patients. One year later, McLeod reported a case series of 8 patients who presented dramatic reductions in their symptoms and improvement in functioning after receiving chromium supplement monotherapy. Patients were diagnosed with various treatment-resistant mood disorders (2 patients with MDD, 3 with dysthymic disorder, 2 with bipolar II disorder and one with depressive disorder not otherwise specified). In all cases, a remarkably rapid onset of clinical response was observed, as well as a rapid return of mood symptoms after the supplementation was discontinued. Single-blind trials of substitution of chromium with other supplements confirmed specificity of the response to chromium. Moreover, response to chromium was strongly associated with the presence of carbohydrate craving and hyperphagia at baseline (McLeod and Golden, 2000).

Based on the case reports by McLeod, Davidson et al. (2003) conducted a small, placebo-controlled, double-blind pilot study in 15 patients with atypical major depression. Ten patients received chromium picolinate (initial dose of 400 µg/day, increased to 600 µg/day after 2 weeks) and 5 patients received placebo for 8 weeks. Response rates were 70% for chromium vs 0% for placebo ( $p = .02$ ), and remission rates were 60% for chromium vs 0% for placebo ( $p = .04$ ). A 50% reduction in Hamilton Rating Scale for Depression (HAM-D) score was evident as early as week 2 in the patients receiving chromium. Treatment was well tolerated; two patients reported insomnia. The drop-out rate was low (13%), compared to the more common rates of 25%–35% seen in most antidepressant trials. The high completion rate may, however, raise questions about the generalizability of the results of the study.

[Docherty et al. \(2005\)](#) conducted a double-blind, multi-center, 8 week study to replicate and expand Davidson's findings in a large cohort. Patients (N = 113) with atypical depression were randomized 2:1 to receive 600 µg/day of chromium picolinate or placebo. The authors found no significant differences in efficacy, with both groups showing significant improvement in total HAM-D scores. However, the group receiving chromium showed significant improvement compared with the placebo group in 4 specific HAM-D 29 items: increased appetite, increased eating, carbohydrate craving, and diurnal mood variation. Additionally, supplemental analyses of a subset of patients with high carbohydrate craving (N = 41) showed that patients who received chromium had a significantly greater response rate compared to the placebo group (65% vs 33%;  $p < 0.05$ ) and a significantly greater improvement on the HAM-D items related to increased appetite and eating, carbohydrate craving, and genital symptoms. While the study did not replicate Davidson et al.'s positive results, it demonstrated that chromium administration produced significant improvement in eating-related atypical symptoms of depression, and that in a subpopulation of patients with high carbohydrate craving the treatment resulted in an overall significant improvement compared with placebo. Study limitations included the lack of a placebo run-in period, the absence of a minimum duration or severity of depression, and the enrollment of patients with different diagnoses (major depressive disorder, dysthymia, and depression NOS), but overall the findings suggested efficacy of chromium on carbohydrate craving and appetite regulation and partly supported its use in atypical depression (see [Table 2](#) for summary of selected trials).

#### 4.3. Safety and tolerability

Chromium dietary supplements are generally well tolerated and safe, particularly in oral formulations within the dosage range normally used. Supplements are available as chromium chloride, chromium nicotinate, chromium picolinate, high-chromium yeast, and chromium citrate. Chromium picolinate seems to be the best tolerated form and one of the more easily absorbed in humans. Over the past 3 decades, there have been no reports of chromium toxicity in any chromium supplement

studies that used trivalent chromium ([Duncan, 1999](#)). Moreover, preclinical studies showed that the addition of chromium picolinate to the diet of rats is not associated with toxicity even at doses greater than a thousand times the usual human intake ([Anderson et al., 1997a,b](#)). The Institute of Medicine reviewed in 2001 the safety information on chromium and concluded that chromium picolinate is safe when used in a way consistent with published clinical data, up to 1.6 mg/day of chromium picolinate (or 200 µg/day of trivalent chromium) for three to six months ([Institute of Medicine, 2001](#)). The most commonly reported side effects with chromium supplementation include initial insomnia, increased and vivid dreams, tremor, and mild psychomotor activation. One patient in the case series of [McLeod and Golden \(2000\)](#) developed uric acid renal stones but a cause–effect relationship was not clearly established.

There are no data regarding the safety of therapeutic doses of chromium picolinate in pregnant and nursing women, and these individuals should exercise caution when considering chromium supplementation for mood disorders. There is also little information about the safety of long-term use.

#### 4.4. Recommendations

There is encouraging evidence that chromium is effective for atypical depression, particularly with regard to increased appetite and carbohydrate craving. Recommended doses of chromium picolinate are in the range of 400 to 600 µg/day, and should be taken in the morning because of possible interference with sleep. The dose of 400 µg was sufficient to alter brain serotonin activity in an experimental study on healthy volunteers who received chromium picolinate for 7 days, and is considered the biologically active daily dose in well-nourished individuals. Chromium is often found in multi-vitamin and multi-mineral dietary supplements, in doses ranging from 50 to 400 µg/day, and some dietary supplements may include other forms of chromium.

Chromium seems to have a relatively benign side-effect profile, although given the risk of cycling, caution should be used in patients who have bipolar disorder.

The literature suggests that chromium picolinate deserves further controlled studies to confirm its efficacy as monotherapy

**Table 2**  
Selected clinical trials of chromium.

Authors (year)	Treatment	Study design	Study length	Sample size and characteristics	Outcome measures/results
<a href="#">Davidson et al. (2003)</a>	Chromium picolinate, 600 µg/day vs placebo	Double-blind, randomized, placebo-controlled	8 weeks	N = 15; atypical depression (MDD)	Significant difference in response rates (70% vs 0%, $p = .02$ ) and remission rates (60% vs 0%, $p = .04$ ) between chromium and placebo
<a href="#">Docherty et al. (2005)</a>	Chromium picolinate, 600 µg/day vs placebo	Multicenter, double-blind, randomized, placebo-controlled	8 weeks	N = 113; atypical depression (MDD, Dysthymia, Depression NOS)	NS difference in reduction of HAM-D score and in response rates (46% vs 43%, $p = .82$ ) between chromium and placebo groups. However, in a subset of patients with high carbohydrate craving (N = 41), response rates were higher with chromium than placebo
<a href="#">McLeod and Golden (2000)</a>	Chromium picolinate, 400–600 µg/day	Case series, single-blind	Variable treatment periods	N = 8; resistant mood disorder (MDD, BD II, Dysthymia, Depression NOS)	All patients experienced marked and rapid improvement, with return of symptoms after discontinuation of chromium. Better response was associated with high carbohydrate craving and hyperphagia at baseline.

MDD: major depressive disorder; BD II: bipolar disorder type II; NS: non significant.

and as augmentation therapy, particularly in atypical depression. Given the overlap between atypical depression and seasonal affective disorder (Mischoulon et al., 2010), a possible role for chromium in SAD should be investigated as well. Longer-term continuation treatment also merits investigation.

## 5. 5-Hydroxytryptophan

5-Hydroxytryptophan (5-HTP) is an aromatic amino acid produced by the body from the essential amino acid L-tryptophan and involved in the synthesis of serotonin. It is produced commercially by extraction from the seeds of the African plant *Griffonia simplicifolia*, and is typically available as the L-enantiomer, where most of the biological activity resides. 5-HTP has been used clinically for over 30 years for the treatment of depression and a wide variety of conditions, including fibromyalgia, insomnia, binge eating associated with obesity, cerebellar ataxia, and chronic headaches.

The clinical activity of 5-HTP is believed to be primarily due to its ability to act as a precursor of serotonin synthesis and increase CNS levels of serotonin. Most studies of the use of 5-HTP for depression were conducted 20 or more years ago, at a time when there was a great interest in the serotonin hypothesis of depression. It appears that, after the first SSRI, fluoxetine, was approved in the US in 1987, and the introduction of other SSRIs quickly followed, research on 5-HTP became less compelling to investigators. Moreover, enthusiasm for 5-HTP was dampened by the concern about its possible association with the potentially fatal eosinophilia-myalgia syndrome, following the outbreak of cases reported in 1989 and 1990 after the ingestion of contaminated L-tryptophan. This too may have contributed to a decline in research on 5-HTP. However, in view of the increasing trend by patients and clinicians towards the use of “natural alternatives” to the FDA-approved antidepressants and the encouraging recent reviews of the safety of 5-HTP, it is worthwhile to re-examine the evidence regarding 5-HTP for treatment of depression.

### 5.1. Mechanisms of action

5-HTP is the intermediate metabolite of L-tryptophan in the production of serotonin. The body absorbs tryptophan, converts it to 5-HTP and then into serotonin both centrally and peripherally. A normal Western diet contains about 0.5 g of tryptophan daily, of which only 2–3% is used in central serotonin production. An increase in dietary tryptophan increases the amount transported across the blood–brain barrier and eventually transformed into serotonin. Both supplements of L-tryptophan and 5-HTP have been used in the treatment of depression, but the use of 5-HTP may offer the advantage of bypassing the conversion of L-tryptophan into 5-HTP by the enzyme tryptophan hydroxylase, which is the rate-limiting step in the synthesis of serotonin. Tryptophan hydroxylase can be inhibited by numerous factors, including stress, insulin resistance, vitamin B6 deficiency, and insufficient magnesium. In addition, these same factors can increase the conversion of L-tryptophan to kynurenine via tryptophan 2,3-dioxygenase, making L-tryptophan unavailable for serotonin production. Moreover, 5-HTP easily crosses the blood–brain barrier, and unlike L-tryptophan, does not

require a transport molecule to enter the central nervous system (Green et al., 1980; Maes et al., 1990).

Besides serotonin, other neurotransmitters and hormones, such as melatonin, dopamine, norepinephrine, and beta-endorphin have also been shown to increase following oral administration of 5-HTP (Birdsall, 1998; Den Boer and Westenberg, 1990; Guilleminault et al., 1973; van Praag and Lemus, 1986). All of these compounds are thought to be involved in the regulation of mood as well as sleep and may represent mechanistic pathways stimulated by 5-HTP administration.

### 5.2. Efficacy

There are approximately 27 published clinical studies that evaluate the efficacy of 5-HTP for treatment of depression, of which at least 8 are double-blind placebo-controlled studies and 4 used an active comparator. 5-HTP demonstrated superiority to placebo in 7 of 11 placebo-controlled studies. However, the sample sizes in all these studies were small and only 6 of them were able to show statistical significance. Of these, one was a monotherapy study (van Praag et al., 1972), one was a cross-over relapse prevention study (van Praag and de Haan, 1981), three were augmentation studies with nialamide (Alino et al., 1976), clomipramine (Nardini et al., 1983), or tryptophan (Quadbeck et al., 1984), and one tested a 5-HTP/dopamine agonist combination against placebo, rather than 5-HTP alone (Rousseau, 1987) (see Table 3 for summary of selected trials).

Van Praag et al. (1972) conducted a small trial with 10 patients affected by severe depression. Subjects were randomized in a double-blind manner to receive 5-HTP or placebo for three weeks, followed by two weeks of placebo. The dose of 5-HTP ranged from 200 to 3000 mg/day. The group receiving 5-HTP showed a mean decrease in HAM-D score of 35% vs a 6% increase for the placebo group ( $t = 2.37$ ,  $p = .05$ ). Three out of 5 patients with 5-HTP were rated as definitely improved, compared with none in the placebo group; two patients in the placebo group reported a worsening of their symptomatology, but none did so in the treatment group. In a subsequent study, van Praag and de Haan (1981) studied relapse rates in a double-blind cross-over trial with 20 patients (14 with MDD, and 6 with bipolar disorder) followed for 2 years, including 1 year on 5-HTP therapy. The 5-HTP-treated group had significantly fewer relapses (6 out of 20 patients) compared to the placebo group (17 out of 20).

Of the augmentation studies that showed a statistically significant superiority of 5-HTP against placebo, the first one (Alino et al., 1976) included 30 psychiatric inpatients diagnosed with “endogenous depression”, randomized in a double-blind manner to receive the MAOI nialamide and 5-HTP or nialamide and placebo. After 15 days, the group exposed to the combination treatment had a mean HAM-D reduction of 58% vs 39% for the group receiving nialamide plus placebo. Twelve of 14 patients were rated as improved or in complete remission, compared with only 6 of 15 in the placebo group.

Nardini et al. (1983) compared the combination of clomipramine and 5-HTP against clomipramine and placebo in a 4-week trial. Of the 24 patients who completed the trial, 13 were given augmentation with 5-HTP and 11 received



**Table 3**

Selected clinical trials of 5-HTP.

Authors (year)	Treatment	Study design	Study length	Sample size and characteristics	Outcome measures/results
Alino et al. (1976)	5-HTP (50–300 mg/day) vs placebo Augmentation of nialamide	Double-blind, randomized, placebo-controlled	15–20 days	N = 30, inpatients with unipolar depression	Significantly greater reduction in HAM-D on 5-HTP vs placebo after 15 days (58% vs 39%). 12/14 markedly improved on 5-HTP vs 6/15 on placebo
Angst et al. (1977)	5-HTP (200–1200 mg/day) vs imipramine	Double-blind, randomized	20 days	N = 30, with endogenous depression	NS difference in improvement between 5-HTP and imipramine
Brodie et al. (1973)	5-HTP (250–3250 mg/day) vs 5-HTP and PDI	Double-blind, non randomized	1–15 days	N = 7, with psychotic depression (N = 6) and schizoaffective disorder (N = 1)	1/7 improved. No significant difference in the two groups
Nardini et al. (1983)	5-HTP (300 mg/day) vs placebo Augmentation of clomipramine	Double-blind, randomized, placebo-controlled	4 weeks	N = 26, with unipolar depression	Significantly greater reduction in HAM-D on 5-HTP vs placebo (56% vs 41%). 7/13 markedly improved on 5-HTP vs 4/11 on placebo; 2/11 worsened in augmentation with placebo
Nolen et al. (1985)	5-HTP (20–200 mg/day) vs tranylcypromine	Open-label, cross-over	4 weeks	N = 44, with treatment-resistant depression	5-HTP significantly less effective than tranylcypromine (0/17 improved on 5HTP vs 15/26 on tranylcypromine)
Nolen et al. (1988)	5-HTP (20–200 mg/day) vs tranylcypromine vs nomifensine	Double-blind and open-label, cross-over	3 weeks	N = 47, with treatment-resistant depression	5-HTP significantly less effective than tranylcypromine, non significant difference vs nomifensine
Poldinger et al. (1991)	5-HTP (300 mg/day) vs fluvoxamine	Double-blind, randomized	6 weeks	N = 69, with unipolar depression	61% reduction in HAM-D in the 5-HTP group vs 56% in the placebo group (NS)
Quadbeck et al. (1984)	5-HTP (75–150 mg/day) and tryptophan vs tryptophan vs low-dose nomifensine	Double-blind, randomized	3 weeks	N = 24, with unipolar depression	Significantly greater reduction in HAM-D on 5-HTP and tryptophan (61%) vs tryptophan (38%) and nomifensine (27%)
Rousseau (1987)	5-HTP (100 mg/day) and dihydroergocristine vs placebo	Double-blind, randomized, placebo-controlled	60 days	N = 50, elderly unipolar depressed patients	12% reduction in HAM-D in the 5-HTP group vs 1% increase in the placebo group
Van Praag et al. (1972)	5-HTP (200–300 mg/day) vs placebo	Double-blind, randomized, placebo-controlled	5 weeks (3 weeks on 5-HTP or pbo followed by 2 weeks on pbo)	N = 10, severely depressed inpatients (unipolar and bipolar)	35% reduction in HAM-D in the 5-HTP group vs 6% increase in the placebo group. 3/5 definitely improved on 5-HTP vs 0/5 on pbo; 2/5 worsened on pbo
Van Praag and de Haan (1981)	5-HTP (200 mg/day) vs placebo	Double-blind, cross-over, relapse prevention	2 years (1 year on 5-HTP)	N = 20, with unipolar (N = 14) and bipolar (N = 6) depression	Significantly fewer relapses on 5-HTP (6/20) vs placebo (17/20)

HAM-D: Hamilton Rating Scale for Depression; PDI: peripheral decarboxylase inhibitor; NS: non significant.

placebo. The 5-HTP group showed a mean decrease in HAM-D score of 56%, compared to a 41% decrease in the placebo group. [Quadbeck et al. \(1984\)](#) compared three groups of 8 patients, assigned to either tryptophan, tryptophan plus 5-HTP, or low dose of the norepinephrine–dopamine reuptake inhibitor nomifensine. The group given 5-HTP and tryptophan showed the greatest improvement, with a mean HAM-D decrease of 61% vs 38% for tryptophan alone and 27% for nomifensine. [Rousseau \(1987\)](#) carried out a double-blind controlled trial in which they treated 50 elderly depressed patients with a combination of 3 mg of the ergot alkaloid dihydroergocristine plus 100 mg of 5-HTP, or placebo for 60 days. The drug combination resulted in statistically significant improvements in depressive state and psychic performance, with a rather small mean HAM-D reduction of 12%, whereas no change was observed in the placebo group.

Among the comparison studies, two showed that 5-HTP performed equally to the active comparators imipramine ([Angst et al., 1977](#)) or fluvoxamine ([Poldinger et al., 1991](#)). However, both studies lacked placebo arms, making their

interpretation difficult. Two cross-over trials comparing 5-HTP against tranylcypromine in treatment-resistant depression found that 5-HTP was less effective ([Nolen et al., 1985](#); [Nolen et al., 1988](#)). One study compared 5-HTP alone vs 5-HTP plus a peripheral decarboxylase inhibitor (PDI) in patients with psychotic depression, with neither group showing improvement ([Brodie et al., 1973](#)). So far there are no published reports comparing 5-HTP against newer antidepressants such as SSRIs.

Other studies include open-label trials with variable results that are largely uninterpretable given the heterogeneity of the studies in terms of design, duration, dose and patient diagnoses (including MDD, bipolar depression, and treatment-resistant depression).

Doses of 5-HTP in the studies reviewed ranged from 20 to 3250 mg/day, with the majority administering between 200 and 300 mg/day. Patients that responded to 5-HTP often noticed improvement of depressive symptoms within two weeks.

Overall, results from the published trials suggest that 5-HTP may have some efficacy in the treatment of depression and may

deserve to be evaluated in more rigorous studies in order to conclusively establish its effectiveness, both as monotherapy and as augmentation. A 2002 systematic review (Shaw et al., 2002) of published clinical trials in which 5-HTP and L-tryptophan were used in depression found that only 2 out of the 108 examined trials were of sufficient quality to meet the inclusion criteria for a meta-analysis. Studies were deemed eligible if they were randomized, placebo-controlled, included only patients with unipolar depression or dysthymia, used 5-HTP or L-tryptophan as monotherapy, and assessed clinical outcome by symptoms scale measurements. Of the two studies included in the meta-analysis (total N=64), one used L-tryptophan (Thomson et al., 1982), and one used 5-HTP (van Praag et al., 1972).

### 5.3. Safety and tolerability

The most common adverse effects reported with 5-HTP are gastrointestinal and include nausea, vomiting, and diarrhea. Generally, oral doses of 200–300 mg/day 5-HTP have been well tolerated. Gastrointestinal effects are usually moderate and often abate or disappear once a steady dosage is achieved. A study comparing 5-HTP to 5-HTP plus a peripheral decarboxylase inhibitor (PDI) found that gastrointestinal side effects were dose-dependent and occurred more frequently in patients receiving 5-HTP alone (Brodie et al., 1973). This may be due to the peripheral conversion of 5-HTP to serotonin, which increases gut motility, and is blocked by PDIs (Brodie et al., 1973). Less common side effects may also include headache, insomnia, and palpitations.

A major concern regarding 5-HTP has been the possibility of the development of eosinophilia–myalgia syndrome (EMS). In 1989 and 1990, ingestion of contaminated supplements of L-tryptophan caused EMS in over 1500 people and resulted in at least 38 deaths (FDA, 1998). The FDA subsequently banned the sale of over-the-counter tryptophan. The contamination identified in certain batches of L-tryptophan was attributed to production methods that used bacterial fermentation and subsequent inadequate filtration. Although 5-HTP is currently produced by extraction from plant sources and that kind of contamination is unlikely to occur, these cases sparked fears that 5-HTP might also cause EMS. In August 1998, the FDA reported that only 10 cases of EMS possibly associated with 5-HTP had been documented worldwide, none resulting in death (FDA, 1998), and no new cases of EMS have since been reported. However, subsequent authors reviewing the safety of 5-HTP noted that none of these cases has been definitively linked to 5-HTP, and criticized the methods of the studies that reported the presence of the toxic contaminant in 5-HTP (Das et al., 2004).

Another potential safety concern is the possibility that 5-HTP, when taken in combination with a SSRI or MAOI antidepressant, may cause serotonin syndrome. This syndrome is characterized by hypertension, hyperthermia, flushing, hyperreflexia, dizziness, disorientation, and myoclonus. Serotonin syndrome may theoretically occur with any drug that affects the serotonin system, and has been reported in patients taking L-tryptophan together with MAOIs or fluoxetine (Lane and Baldwin, 1997). To our knowledge, however, serotonin syndrome has never been reported in humans in association with 5-HTP, either as monotherapy or in combination with other medications,

including TCAs, MAOIs and L-tryptophan (Alino et al., 1976; Das et al., 2004; Kline and Sacks, 1980; Nardini et al., 1983; Nicolodi and Sicuteri, 1996; Quadbeck et al., 1984). We found only one study in which 5-HTP was used in association with fluoxetine. Single doses of 5-HTP (200 mg) were administered to 26 patients with MDD or obsessive–compulsive disorder taking fluoxetine, none of whom developed signs or symptoms of serotonin syndrome (Meltzer et al., 1997).

Taken together, these safety findings are encouraging but must be considered preliminary, given the small numbers of patients exposed in these studies. 5-HTP should therefore be used with caution in patients currently being treated with either an SSRI or MAOI, and vigilance should always be advised when using 5-HTP, either as monotherapy or combination agent.

There are no adequate, well-controlled trials on the use of 5-HTP in pregnant women, nor any systematic studies evaluating long-term side effects of 5-HTP.

### 5.4. Recommendations

The doses of 5-HTP used in the reviewed studies ranged from 20 to 3250 mg/day, more often from 200 to 300 mg/day, with dose scheduling ranging twice- to 4-times-per-day. The recommended dosing frequency was 3-times-per-day in a recent review article (Birdsall, 1998), as 5-HTP has a relatively short half-life ( $4.3 \pm 2.8$  h; Westenberg et al., 1982). Moreover, two studies have found a lower incidence of nausea with smaller doses (van Hiele, 1980; Magnussen and Van Woert, 1982), suggesting that the rate of adverse events may be dose-dependent. 5-HTP is well absorbed orally, and its absorption is not affected by other amino acids; it may therefore be taken with meals without reducing effectiveness. Initial dosage is usually 50 mg three times a day with meals, and can be titrated upward if clinical response is inadequate after two weeks.

The co-administration of 5-HTP with the peripheral decarboxylase inhibitor carbidopa resulted in a 14-fold increase in 5-HTP plasma levels in a recent study of healthy volunteers (Gijsman et al., 2002). However, there seems to be no consensus as to whether the addition of carbidopa increases the effect of 5-HTP (Zmilacher et al., 1988).

Overall, results from the clinical studies and safety reports suggest that 5-HTP supplementation may have at least some antidepressant efficacy and generally good tolerability. It is difficult, however, to draw definitive conclusions from the current evidence. Turner and colleagues recently concluded that 5-HTP supplementation deserves reconsideration as a possible addition to the antidepressant armamentarium, but it may be still premature to recommend its widespread clinical use until more extensive clinical trials further address 5-HTP's efficacy and safety (Turner et al., 2006).

## 6. Inositol

Inositol is a sugar alcohol and a structural isomer of glucose, ubiquitous in biologic organisms and located primarily within cell membranes. Of its nine different isomeric compositions, myo-inositol is the most abundant biologically active stereoisomer in the human body, comprising 95% of total free inositol (Moore et al., 1999).

Inositol is present in a variety of foods, particularly beans, grains, nuts, and many fruits ([Clements and Darnell, 1980](#)). The average adult human consumes about 1 g/day of inositol ([Belmaker and Levine, 2008](#)). Inositol is usually classified as a member of the vitamin B family, specifically vitamin B8.

Inositol is an important growth factor for human cells ([Ross, 1991](#)), acting in the synthesis of membrane phospholipids and as a precursor in the phosphatidylinositol (PI) cycle ([Baraban et al., 1989](#)). The PI cycle is the second messenger system for numerous neurotransmitter receptors, including cholinergic muscarinic, alpha 1 noradrenergic, serotonergic 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub>, and dopaminergic D1 receptors, which are involved in several psychiatric conditions. The potential importance of inositol in psychiatric disorders is thereby evident when one considers the number of receptor types/subtypes that interact with this signal transduction pathway.

### 6.1. Mechanism of action

As a precursor of the PI cycle, inositol is used for the production of inositol triphosphate (IP<sub>3</sub>) and diacylglycerol (DAG), important second messengers that allow cell surface receptors for neurotransmitters to affect intracellular processes. The initial rationale for treating depression by inositol supplementation came from the finding of decreased inositol in the cerebrospinal fluid (CSF) of depressed patients ([Barkai et al., 1978](#)). Subsequent studies, however, did not replicate this finding and found that baseline CSF inositol did not predict response to inositol treatment ([Levine et al., 1996a,b](#)). Post-mortem studies have also shown that levels of inositol in the frontal cortex of suicide victims and patients with bipolar disorder are lower compared with normal controls ([Shimon et al., 1997](#)). Magnetic resonance spectroscopy (MRS) studies have also examined inositol in adults. [Frey et al. \(1998\)](#) reported reduced myo-inositol concentrations in the frontal lobes of untreated depressed bipolar and unipolar patients compared with healthy controls. [Moore et al. \(1999\)](#) found a reduction of myo-inositol concentrations in the frontal lobe of medicated depressed bipolar patients, following both acute (5–7 days) and chronic (3–4 weeks) lithium treatment. However, MRS studies in MDD have yielded mixed results regarding changes of myo-inositol concentration in particular areas of the cortex of both medicated and unmedicated patients (reviewed in [Kim et al., 2005](#)).

The anti-manic effect of lithium may be associated with a reduction of inositol levels ([Allison and Stewart, 1971](#); [Berridge et al., 1989](#)), and chronic treatment with either lithium or sodium valproate may normalize PI cycle functioning ([Silverstone et al., 2002](#)). Mood stabilizers appear to share a common mechanism of action that involves stabilization of inositol signaling ([Cheng et al., 2005](#); [Williams et al., 2002](#); [Wolfson et al., 2000](#)). The hypothesis of a possible excess of inositol in mania suggests its possible deficit in depression, and implementation of dietary inositol might therefore be therapeutic in depression. Administration of inositol has indeed been reported to increase inositol concentration within the CNS in humans ([Levine et al., 1993](#); [Turner et al., 2006](#)).

Additional evidence for the antidepressant efficacy of inositol comes from double-blind clinical trials examining efficacy in panic and obsessive-compulsive disorder ([Fux et al., 1996](#); [Levine, 1997](#)). Moreover, data from animal models of depression

have shown that inositol is active ([Einat et al., 1999](#); [Porsolt et al., 1978](#)). In a small randomized, double-blind cross-over study, inositol was used in healthy volunteers to test its effect on mood and anxiety ([Levine et al., 1994](#)). A single dose of inositol 12 g or placebo was administered to 11 subjects. Inositol reduced sadness, hostility, tension and fatigue compared to placebo over 6 h; the effect was significant in subjects who presented with high baseline depression or tension scores ([Einat et al., 1999](#)).

Considering the available evidence, a decrease in brain inositol, which adversely affects the PI second messenger system, could in turn result in mood changes or full-blown mood disorders. Dietary supplementation with inositol might therefore improve the functioning of the PI system, thus alleviating depressive symptoms.

### 6.2. Efficacy

Double-blind, controlled trials of inositol in depressed adults offer conflicting findings. There are approximately 6 published clinical trials of inositol for outpatient treatment of depression, of which 5 are placebo-controlled. Only one study used inositol as monotherapy ([Levine et al., 1995](#)), and the others augmented conventional antidepressants and mood stabilizers with inositol. Two studies included only patients with MDD ([Levine et al., 1999](#); [Nemets et al., 1999](#)), one study included patients with unipolar and bipolar depression ([Levine et al., 1994](#)), and the remaining studies involved patients with bipolar disorder who were currently depressed. Inositol outperformed placebo in 3 of the 5 controlled studies, but all sample sizes were small and statistical significance was reached in only one study (see [Table 4](#) for summary of selected trials).

[Levine et al. \(1995\)](#) conducted a randomized, double-blind, 4-week study of 27 adults with MDD or bipolar disorder who were depressed and had failed to respond to, or had not tolerated, a trial with conventional antidepressants. Subjects were given either inositol 12 g/day as monotherapy or placebo. Treatment with inositol resulted in significantly greater improvement in HAM-D score at 4 weeks compared to placebo ( $p = .04$ ). No difference was evident at week 2. The same authors conducted a double-blind, placebo-controlled, augmentation study on 27 patients with MDD. Patients were randomized to receive a combination of SSRI (fluvoxamine, fluoxetine or paroxetine) and inositol 12 g/day or placebo. No significant difference was found between the two treatment groups ([Levine et al., 1999](#)).

Similarly, [Nemets et al. \(1999\)](#) conducted a double-blind, placebo-controlled study of inositol as augmentation in 42 patients with MDD who had failed to respond to at least 3 weeks of treatment with an SSRI at clinically adequate dose (150 mg fluvoxamine, 20 mg fluoxetine, 20 mg paroxetine). Patients were randomly assigned to receive adjunctive inositol 12 g/day or placebo for 4 weeks. Inositol was found to have no effect in augmenting the response to SSRI therapy compared to placebo ([Levine et al., 1999](#)).

The studies of inositol as an adjunctive treatment in bipolar depressed subjects have suggested a modest clinical efficacy. In a randomized double-blind study ([Chengappa et al., 2000](#)), 24 adults diagnosed with bipolar depression (21 bipolar I, 3 bipolar II) were given either inositol 12 g/day or placebo as add-on treatment to current medication for 6 weeks. Mood

**Table 4**

Selected clinical trials of inositol.

Authors (year)	Treatment	Study design	Study length	Sample size and characteristics	Outcome measures/results
Chengappa et al. (2000)	Inositol (12 g/day) vs placebo Add-on to mood stabilizers (± antidepressants)	Double-blind, randomized, placebo-controlled	6 weeks	N = 24, with bipolar depression (BD I (N = 21) or BD II (N = 3))	Higher response rates with inositol vs placebo (50% vs 30%, NS)
Evins et al. (2006)	Inositol (5–20 g/day) vs placebo Add-on to mood stabilizers (± antidepressants)	Double-blind, randomized, placebo-controlled	6 weeks (+ 8 weeks of open-label follow-up)	N = 17, with bipolar depression (BD I (N = 16) or BD II (N = 1))	4/9 on inositol responded vs 0 on placebo (trend) 2/9 on inositol worsened vs 0 on placebo
Levine et al. (1995)	Inositol (12 g/day) vs placebo	Double-blind, randomized, placebo-controlled	4 weeks	N = 27, with unipolar and bipolar depression who failed to respond to, or had not tolerated, a trial with conventional antidepressants.	Significantly greater improvement in HAM-D with inositol vs placebo
Levine et al. (1999)	Inositol (12 g/day) vs placebo Augmentation of SSRI	Double-blind, randomized, placebo-controlled	4 weeks	N = 27, with MDD	NS difference between the two groups
Nemets et al. (1999)	Inositol (12 g/day) vs placebo Augmentation of SSRI	Double-blind, randomized, placebo-controlled	4 weeks	N = 42, with treatment-resistant MDD	NS difference between the two groups
Nierenberg et al. (2006)	Inositol (10–25 g/day) vs lamotrigine vs risperidone Add-on to mood stabilizers and antidepressant(s)	Open-label, randomized	16 weeks	N = 17, with bipolar depression, not responsive to a combination of mood stabilizers plus at least one antidepressant	Recovery rates of 17% with inositol, 24% with lamotrigine, 5% with risperidone (NS between-group differences)

MDD: major depressive disorder; BD I: bipolar disorder type I; BD II: bipolar disorder type II; NS: non significant.

stabilizers at study entry were continued unchanged; 10 patients who had also failed to respond to conventional antidepressants continued their medications unchanged. At the end of the study, 50% of the patients treated with inositol responded with a 50% or greater decrease in their baseline HAM-D scale score and a CGI score of “much” or “very much” improved, compared to 30% of the patients assigned to placebo. The difference between the treatment groups was not significant, but showed some efficacy of inositol for bipolar depression, together with good tolerability. In an extended open-label follow-up up to 24 weeks, 5 of the 6 inositol responders maintained good response while continuing on inositol; one patient developed mania. Of the 3 placebo responders, 2 relapsed within 2 to 3 weeks and one was lost to follow-up (Nemets et al., 1999).

In another double-blind controlled study (Evins et al., 2006), 17 depressed bipolar patients (16 bipolar I, one bipolar II), were randomized to receive either inositol 5 to 20 g/day or placebo as adjunctive treatment. Subjects were failing to respond to an adequate therapeutic regimen with mood stabilizers for at least 2 weeks, and were allowed to continue their concomitant medications (including antidepressants, antipsychotics, and benzodiazepines) if they were at stable doses for at least the last 2 weeks. Patients in the placebo group had significantly higher mean HAM-D scores at baseline compared to the inositol group. Four of the 9 subjects who received inositol responded, vs none from the placebo group, though the difference was not significant ( $p = .053$ ). Two patients in the inositol group had a worsening of depressive symptoms, compared to none in the placebo group.

Nierenberg et al. (2006) conducted a comparative open-label add-on study in depressed bipolar patients not responsive

to a combination of mood stabilizers plus at least one antidepressant. Sixty-six subjects with bipolar I or bipolar II disorder were randomized to receive lamotrigine, risperidone, or inositol (target dose 10–25 mg) added to their regular treatment for up to 16 weeks. The primary outcome measure was rate of recovery or full remission, defined as the absence of significant symptoms for 8 weeks. There were no significant between-group differences; however, results indicated that lamotrigine was superior to inositol and risperidone in improving treatment-resistant bipolar depression, and inositol outperformed risperidone. Recovery rate was 24% with lamotrigine, 17% with inositol, and 5%, with risperidone. The authors concluded that adjunctive lamotrigine, as well as inositol, might have potential usefulness among difficult-to-treat patients (Evins et al., 2006).

Other studies showed that inositol is also effective for panic disorder, OCD, and bulimia nervosa, suggesting a broad spectrum of action which resembles that of SSRIs (reviewed in Belmaker and Levine, 2008).

### 6.3. Safety and tolerability

Inositol is generally well tolerated and appears to have a favorable safety profile. Side effects reported in the reviewed clinical trials, at doses of inositol ranging from 6 to 25 g/day, include mild increases in plasma glucose, flatus, nausea, sleepiness, insomnia, dizziness and headache. No patients dropped out from the trials due to side effects. However, there have been case reports of inositol-induced mania in bipolar depressed patients (Levine et al., 1996a,b). To date, there are no reported cases of toxicity from inositol supplementation, and no

drug–drug interactions in studies where inositol was co-administered with FDA-approved medications.

Inositol supplementation should not be recommended for pregnant women, given the risk of inducing uterine contractions (Phaneuf et al., 1995).

#### 6.4. Recommendations

Inositol is a nutritional supplement that has been suggested as a treatment for depressive disorders. Most of the studies have been conducted on depressed bipolar patients receiving inositol as an augmentation for mood stabilizers and antidepressants. Findings suggest good tolerability and at least some efficacy for inositol in alleviating depressive symptoms. While the two studies on unipolar depression were negative, further studies with larger sample sizes are needed to draw more definitive conclusions.

Recommended doses of inositol fall between 6 and 20 g/day, usually 12 g/day, divided in two- to four-times a day. Twelve grams orally per day has been shown to increase CSF inositol levels by 70% (Levine et al., 1993). Inositol appears to have a relatively benign side-effect profile. Given the potential risk of cycling, care needs to be taken in bipolar patients, who should be advised to use inositol only with a concurrent mood stabilizer.

### 7. Conclusions

The use of alternative medicine in the United States continues to grow in popularity and increasing numbers of patients are asking their psychiatrists about natural alternatives to prescription antidepressants. There are several herbs and dietary supplements that claim to have beneficial effects on depression and are widely used by people with mood disorders. The evidence for their effectiveness, however, is limited for most of them.

While approximately two dozen FDA-approved pharmaceutical agents are available for the treatment of mood disorders, many patients have difficulty tolerating the side effects, do not respond adequately, or eventually lose benefit. Given that many therapeutic herbs and dietary supplements have reportedly fewer side effects, they may provide an alternative treatment or be used to enhance the effect of prescription medications. The recent concern about the true efficacy of standard antidepressants (Khan et al., 2010) is likely to further popular interest in alternative medicine, though this concern applies to natural products as well, given similar study designs and patient populations that participate in these studies.

In this review we gave some attention to four lesser-known potential natural antidepressants, for which promising early trials suggest both efficacy and safety in treating mood disorders. Current research data seem particularly encouraging for the use of *R. rosea* and chromium for specific populations of depressed patients. *R. rosea* can be especially helpful in treating asthenic or lethargic forms of depression. In combination with conventional antidepressants it may alleviate some common side effects, given its positive effects on memory, sexual dysfunction and weight management. Chromium would appear to be particularly valuable in the treatment of atypical depression and potentially seasonal affective disorder, given its efficacy in improving eating-related atypical symptoms of

depression, such as increased appetite and carbohydrate craving. As for inositol, in contrast to its probable lack of efficacy in unipolar depression, preliminary findings suggest that it can be effective when combined with mood stabilizers in the treatment of bipolar depression. As with the other treatments reviewed here, the evidence for the clinical efficacy of 5-HTP is thus far restricted to studies with small samples and briefer than optimal durations, though their preliminary findings have been considered encouraging (Thachil et al., 2007), and more extensive clinical trials are necessary to address questions regarding 5-HTP's efficacy and safety.

More well-designed controlled studies, particularly with larger patient samples, are needed for all these natural medications before any substantive conclusions can be drawn. The evidence available, however, is compelling and these natural products deserve further investigation and consideration as a possible significant addition to the antidepressant armamentarium.

Although all the medications reviewed here have a promising safety profile, care should be taken with patients who are taking multiple medications, including herbs and dietary supplements, in view of the potential risk of adverse drug–drug interactions. Finally, as with all psychotropic agents, natural medications should be used preferably under the supervision of a physician.

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#### Conflicts of interests

Dr. N. Iovieno and Ms. E.D. Dalton declare that they have no conflicts of interest.

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