Adverse Neuropsychiatric Reactions to Herbal and Over-the-Counter "Antidepressants"

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Background: Many unregulated over-the-counter agents for the treatment of depression are now available to patients and consumers. The potential for adverse neuropsychiatric effects with these agents has not been systematically studied in most cases.

Data Sources: The author performed a MEDLINE search on a variety of herbal and nonherbal over-the-counter agents said to be useful in the treatment of depression. The *Physicians' Desk Reference for Herbal Medicines* was also consulted.

Data Synthesis: Although many of the herbal agents said to have benefits in depression appear to be safe, serious neuropsychiatric side effects and interactions have been reported for several over-the-counter "antidepressants." There is reason to suspect underreporting of those adverse events. Moreover, there is very little evidence from systematic studies regarding the potential for drug-drug or herb-drug interactions with these over-the-counter agents. Vitamins and amino acids touted for the treatment of depression are also not without risk.

Conclusion: Although some over-the-counter remedies for depression are probably safe and effective for as-yet unidentified subgroups of depressed individuals, more research is required before these agents can be recommended for routine use. Stricter U.S. Food and Drug Administration oversight of these agents is indicated.

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It is estimated that so-called alternative or complementary medicine is used by about 25% of the general North American population, especially in patients with chronic conditions.[1] The Dietary Supplement Health and Education Act allows so-called dietary supplements to be sold without U.S. Food and Drug Administration (FDA) approval, although they must have a disclaimer on their labels.[2] A product sold in a "health food" store without prescription or FDA regulation may have the aura of safety around it. Unfortunately, this is not always the case, and an increasing number of neuropsychiatric reactions to herbal and "natural" remedies are appearing in the literature. For example, Emmanuel et al.[3] recently reported the occurrence of manic symptoms in a 40-year-old woman with a history of bulimia who was covertly using "herbal products from the health food store" to induce weight loss. The preparation contained ma huang (ephedrine), chromium picolinate, and caffeine. Ma huang consists of the dried, young branchlets of *Ephedra sinica* or related species and contains the well-known sympathomimetic alkaloids ephedrine and pseudoephedrine.[4] Irritability, motor restlessness, and sleeplessness are reported side effects of ma huang.[4] Another herb, *Oenothera biennis* (evening primrose)—sometimes used to treat hyperactivity and premenstrual syndrome[4]—has not been linked with manic reactions, but may have the potential for worsening mania.[1] Of course, most standard antidepressants are known to induce mania or hypomania in susceptible individuals; however, given the unregulated use of over-the-counter remedies, the exposure of patients with high susceptibility to mania may be greater among those who use these remedies than in ordinary psychiatric practice.

In this article, I review the herbal and nonherbal remedies currently sold over the counter with implicit claims of benefit in the treatment of depression. Because these agents do not go through the FDA approval process for drugs, their labeling is supposed to be limited to claims of general "health maintenance" rather than to the treatment of actual "diseases." Because the general public is heavily influenced by nonprofessional advertising claims, I have selected agents for review on the basis of claims in both the nonprofessional and the professional literature. While "herb-drug" interactions are beyond the scope of this article, I will briefly cover some of these issues in relation to St. John's wort. A more exhaustive review of herbal agents in psychiatric practice is provided by Wong et al.[1]

DATA SOURCES

A MEDLINE search (1966–2000) used the search terms *neuropsychiatric* and *adverse effects* for each agent reviewed and was restricted to human subjects. For herbs, both the botanical and common names were used as search terms. A separate search was carried out for each agent using the search term *mania*. In addition, I utilized the *Physicians' Desk Reference [PDR] for Herbal Medi-*

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cines[4] as a guide to the agents that were "indicated" for the treatment of depression and to their reported neuropsychiatric side effects.

DATA SYNTHESIS

Nonherbal Over-the-Counter Remedies for Depression

SAMe. In the past year, *S*-adenosylmethionine (SAMe) became available as a stable, enteric-coated tablet in the United States. Interest in SAMe was fueled, in part, by the appearance of the book *Stop Depression Now* by Richard Brown, M.D., Teodoro Bottiglieri, Ph.D., and Carol Colman.[5] The dust jacket of the book describes SAMe as "the breakthrough supplement that works as well as prescription drugs, in half the time . . . with no side effects." First described by Cantoni in 1953, SAMe is a naturally occurring compound in the human body, formed from methionine and adenosine triphosphate.[6] SAMe occurs in many mammalian tissues, especially liver and brain. After parenteral administration, SAMe crosses the blood-brain barrier, where it seems to have several effects on brain chemistry. SAMe donates an active methyl group to various acceptor molecules, including catecholamines, fatty acids, phospholipids, proteins, and nucleic acids.[6] SAMe appears to increase central turnover of dopamine and serotonin; for example, it increases the main metabolite of central serotonin—5-HIAA (5-hydroxyindoleacetic acid)—in the cerebrospinal fluid.[7]

Most of the early data on SAMe came from studies of parenteral administration. Lipinski et al.[8] carried out an open trial using intravenous SAMe in depressed inpatients. The dose was 200 mg/day for 14 days or until remission. Seven of 9 patients improved, but 2 bipolar patients developed hypomania or mania. In the past decade, a number of studies of oral SAMe have appeared. In an open study of 20 outpatients with major depression,[9] oral SAMe (1200–1600 mg/day) led to improvement in 9 patients. Side effects were mild and transient, with no major neuropsychiatric problems noted. Kagan et al.[10] carried out a randomized, double-blind, placebo-controlled trial of oral SAMe in 15 inpatients with unipolar, nonpsychotic major depression. In the SAMe group (dose = 800 mg b.i.d.), 6 of 9 patients had reductions of more than 50% in Hamilton Rating Scale for Depression (HAM-D) scores, versus only 1 of the 6 placebo patients. Headache was reported in one of the SAMe subjects, and persistent manic symptoms in another patient with no history of mania. (Note that bipolar patients were excluded from the Kagan et al. study.[10]) The authors themselves acknowledge that the small patient sample limited the strength of their findings.

SAMe has not been studied systematically in well-defined samples of psychotic or bipolar depressed patients; hence, conclusions about its safety and efficacy in these populations are premature. Neither do we have data from controlled studies on long-term (6 months and longer) outcome with SAMe in unipolar depression. The high switch rate in bipolar patients suggests that SAMe should not be used as monotherapy in bipolar patients. Brown et al.[5] report that SAMe may be safely combined with most other antidepressants (excluding monoamine oxidase inhibitors [MAOIs]) and suggest that SAMe may hasten or enhance the antidepressant effects of conventional medications. However, to my knowledge, no formal studies of safety have been carried out in patients taking SAMe with other (prescribed) antidepressants. Certainly, the putative serotonergic effects of SAMe raise the possibility of a "serotonin syndrome" when this agent is combined with selective serotonin reuptake inhibitors (SSRIs), although I am unaware of any reports that this has occurred. At the very least, patients taking SAMe with SSRIs should be cautioned to report symptoms of confusion, diarrhea, restlessness, sweating, shivering, or myoclonus, which would suggest onset of serotonin syndrome.

DHEA. Dehydroepiandrosterone (DHEA)—a precursor to androgenic steroids—has been widely touted in the lay press as a "fountain of youth" and an aphrodisiac.[11] DHEA is widely available over the counter as a "dietary supplement," although it is not known to have true nutritional value. Some studies have found DHEA to have antidepressant effects in certain populations, e.g., patients with midlife-onset dysthymia[12] and major depression[13]; however, a recent review by Gelenberg[14] concluded that "a role for DHEA remains to be established by rigorous scientific trials."[(p38)]

At least 2 case reports have linked DHEA to manic reactions. One such reaction occurred in an elderly man with no prior psychiatric history or family history of bipolar disorder.[15] Another report[16] involved a 51-year-old man who had begun taking DHEA (50 mg/day) to "increase his energy level" and subsequently developed a severe manic episode with psychotic features. The patient had no history of prior mania, depression, or psychiatric treatment. He required involuntary hospitalization and slowly responded to a combination of haloperidol and divalproex sodium. A MEDLINE search found no additional reports of adverse neuropsychiatric reactions to DHEA. Nevertheless, caution is warranted, given the risk of both mania and psychosis with this agent.

Inositol. Inositol is a simple isomer of glucose and a key metabolic precursor in the phosphatidylinositol cycle.[17] Beneficial effects from oral inositol have been reported in patients with depression, panic attacks, and obsessive-compulsive disorder, while no benefit has been found in patients with schizophrenia, Alzheimer's disease, autism, or attention-deficit/hyperactivity disorder (ADHD).[18] Indeed, there is some suggestion that inositol may aggravate symptoms of ADHD in children.[18] In one placebo-controlled study of inositol (12 g/day) in major depression,[17] overall improvement in HAM-D scores was

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noted with inositol versus placebo. Of the 13 depressed subjects treated with inositol, 4 had bipolar disorder. None of these subjects showed evidence of mania with inositol treatment, despite the absence of a conventional mood stabilizer. However, 7 patients dropped out of the inositol group within 1 week of starting the trial and were not included in the data analysis. Two of these 7 had mild psychotic symptoms, and 1 had weakness and tremor. Subsequently, Levine et al.[19] reported 3 cases of possible inositol-induced mania or hypomania. Two of the patients had histories of recurrent major depression, and 1, a history of bipolar II disorder. Hypomanic symptoms appeared in these cases at inositol doses ranging between 3 and 27 g/day. Although other mechanisms of hypomania were considered by the authors, they concluded that inositol, like conventional antidepressants, may induce mania or hypomania. Thus, while inositol may show some benefits in selected depressed populations, it has the potential to provoke neuropsychiatric side effects in some patients. Nevertheless, a MEDLINE search revealed no additional cases of adverse neuropsychiatric events associated with the clinical use of inositol.

Herbal Over-the-Counter Remedies for Depression

St. John's wort. St. John's wort (*Hypericum perforatum*) has been used worldwide as an antidepressant and is the most extensively studied herbal remedy for the treatment of depression.[1,20] The active ingredient or mechanism of action for St. John's wort remains speculative, although serotonergic effects have been postulated on the basis of in vitro studies.[1] Although it is usually well-tolerated, several anecdotal reports of mania or hypomania have been reported in association with St. John's wort. Schneck[21] described a hypomanic mixed state associated with St. John's wort in a patient who suffered from panic disorder and depression but had no history of bipolar disorder. Similarly, O'Breasail and Argouarch[22] reported 2 cases of individuals with no preexisting history of bipolar disorder who developed hypomanic episodes after taking St. John's wort. Moses and Mallinger[23] reported 3 cases of possible mania induction associated with St. John's wort. The first patient was an elderly woman with a history of recurrent depression, but no bipolar disorder, who developed manic symptoms 2 weeks after starting St. John's wort. Since this patient had also abruptly discontinued her prescribed antidepressants, antidepressant-withdrawal mania cannot be excluded.[24] The other 2 cases included a 53-year-old man with bipolar II disorder and a 61-year-old woman with bipolar I disorder. It is important to note that the 53-year-old man suffered ongoing paranoid and "erotomanic" symptoms for several weeks after discontinuing St. John's wort. The authors speculated that age greater than 50 years may predispose mood-disordered patients to St. John's wort–induced mania.

The potential of St. John's wort to interact with standard, prescribed antidepressants, possibly to produce a "serotonin syndrome," is also a concern. Gordon[25] reported a case in which a female patient taking St. John's wort became groggy, weak, and lethargic shortly after taking a single 20-mg dose of paroxetine. This patient had tolerated St. John's wort and paroxetine separately, suggesting a drug-drug interaction.[26] A MEDLINE search failed to turn up any other reports of adverse neuropsychiatric effects associated with St. John's wort. Nevertheless, the combined use of this herb with other psychotropic medications is not well studied, nor are the effects of St. John's wort in bipolar or psychotically depressed populations clearly known. Until well-designed studies are available, it seems prudent for clinicians to avoid use of St. John's wort in bipolar patients and to warn bipolar patients not to use St. John's wort on their own.

Other herbs said to have antidepressant effects. In addition to St. John's wort, the *PDR for Herbal Medicines*[4] lists 11 herbs or herbal derivatives that are thought useful in the treatment of depression (Table 1). The actual efficacy of these agents is beyond the scope of this paper; however, on the basis of both the *PDR for Herbal Medicines* and a MEDLINE search, these agents are not associated with reports of serious neuropsychiatric side effects or mania. Since all possible search terms (e.g., *anxiety*, *restlessness*) were not utilized, and since the putative active chemical agents of these herbs were not searched separately, it is impossible to rule out some adverse neuropsychiatric side effects from these herbal preparations. (Note that flavonoids are mentioned in 6 of 12 entries under putative active compounds.) In addition, it is quite likely that many adverse reactions to herbal remedies go unreported, since these agents are often used without medical supervision. Furthermore, the potential for "herb-drug" interactions between these remedies and prescribed medications remains almost completely unexplored.

Pharmacokinetic Issues and Herb-Drug Interactions

Ayd has noted that scant data are available on herb-drug interactions and that "all ingested substances have the potential to interact" (F. J. Ayd, Jr., M.D., written communication, May 3, 2000). For example, while the herb ginseng is not promoted specifically as an antidepressant, it is often used as a "quick energy fix."[27] There is at least 1 report[28] of ginseng-induced mania within 4 to 10 days of a patient's interrupting treatment with lithium and amitriptyline; it is unclear to what extent the mania may have reflected an interaction with residual amounts of these prescribed medications. Herb-drug interactions are reviewed in the recent article by Cupp[29] and will not be comprehensively covered here; however, a few comments on St. John's wort are in order.

As Johne et al.[30] have noted, "knowledge about the pharmacokinetics of ingredients and drug interactions of

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Table 1. Herbs Used for Depression[a]

Scientific Name	Common Name	Putative Active Compounds[b]	Neuropsychiatric Side Effects Noted in the *PDR for Herbal Medicines*	Neuropsychiatric Side Effects Based on MEDLINE Search
Anagallis arvensis	Scarlet pimpernel	Triterpene saponins, cucurbitacins, flavonoids, caffeic acid derivatives	None	None
Artemisia vulgaris	Mugwort	1,8-Cineol, sesquiterpene lactones, lipophilic flavonoids, polyynes, hydroxycoumarins	None	None
Cannabis sativa	Marijuana	9-Tetrahydrocannabinol in addition to 60 additional cannabinoids	Euphoric states, exaggerated sensory impressions, alterations in time/space perception, multiform hallucinations; chronic use may lead to apathy and/or "psychic decline"	Associated with de novo psychosis, activation of preexisting psychosis, and other psychiatric syndromes
Corydalis cava	Corydalis	Isoquinoline alkaloids	None	None
Eschscholtzia californica	California poppy	Isoquinoline alkaloids, cyanogenic glycosides	None	None
Hypericum perforatum	St. John's wort	Anthracene derivatives, including hypericin and pseudohypericin; flavonoids; hyperforin	None	At least 6 cases of mania/hypomania reported[21–23]
Melissa officinalis	Lemon balm	Volatile oil containing geranial and numerous other components, glycosides, caffeic acid derivatives, flavonoids, triterpine acids	None	None
Ocimum basilicum (*Basilici aetheroleum*)	Basil	Estragole, linalool, eugenol	None	None
Origanum majorana (*Majoranae herba*)	Marjoram	Flavonoids, arbutin, caffeic acid derivatives, various terpinenes	None	None
Passiflora incarnata	Passionflower	Flavonoids, cyanogenic glycosides	None	None
Strychnos nux-vomica	Nux vomica	Indole alkaloids, including strychnine and brucine; iridoide monoterpines	Restlessness, anxiety, heightened sense perceptions	None
Syzygium cumini	Jambolan	Fatty oil containing oleic acid and/or myristic acid, tannins including corilagin	None	None

[a]From the *Physicians' Desk Reference (PDR) for Herbal Medicines*.[4]
[b]List of active compounds is not exhaustive.

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St. John's wort is poor."[p338] These investigators studied the effects of a *Hypericum* extract from St. John's wort upon the pharmacokinetics of digoxin in healthy volunteers. After 10 days of treatment with the extract, a 25% decrease was found in digoxin area under the curve (AUC), possibly owing to the induction by St. John's wort of the P-glycoprotein drug transporter.[30] Thus, patients taking St. John's wort and digoxin might expect reduced blood levels and/or clinical effects of digoxin. Recently, concern has mounted regarding the effects of St. John's wort on medications used to treat acquired immunodeficiency syndrome/human immunodeficiency virus infection. For example, Piscitelli et al.[31] found that St. John's wort reduced the AUC of indinavir by a mean of 57%—enough, potentially, to cause drug resistance and treatment failure. Since cytochrome P450 3A4 (CYP3A4) is primarily involved in oxidative metabolism of indinavir,[32] it is reasonable to presume that St. John's wort is an inducer of CYP3A4. This could potentially lead to herb-drug interactions with numerous psychotropic agents, including tertiary tricyclics, nefazodone, and triazolobenzodiazepines. On the other hand, St. John's wort does not appear to be a strong inhibitor of either CYP3A4 or CYP2D6.[33] This, of course, does not mean that pharmacodynamic interactions with St. John's wort cannot take place with drugs metabolized through these cytochrome systems, e.g., via potentiation of central nervous system serotonin.[25,26]

Amino Acids and Vitamins

Claims in the lay press often appear regarding supposed antidepressant effects of various amino acids, neurotransmitter precursors, and vitamins, most of which are easily available over the counter. Yet the evidence that these agents are effective for clinically significant depression is quite limited. Reviewing the data on tryptophan, Jones and Stanley[34] concluded that "no consensus has emerged regarding the efficacy of tryptophan in the treatment of depression."[p150] Regarding 5-HTP (5-hydroxytryptophan), the immediate precursor of serotonin, these authors found only modest evidence for antidepressant efficacy. (In 1990, the FDA withdrew L-tryptophan from the market owing to its association with eosinophilia-myalgia syndrome.) More recently, Meyers[35] concluded that it is "difficult to draw firm conclusions regarding the efficacy of neurotransmitter precursors for

treating depression" while acknowledging that these agents "can be helpful in patients with mild or moderate depression."(p64) Use of 5-HTP may be associated with gastrointestinal side effects, while reports exist of toxic reactions to combined tryptophan/SSRI or tryptophan/MAOI treatment.[34]

It is widely recognized that deficiency of folate and various B vitamins (B_6, B_{12}) may be associated with depression and other neuropsychiatric syndromes, as reviewed by Lishman.[36] This does not imply, of course, that ingesting large doses of B vitamins is effective for depression unrelated to vitamin deficiency. On the other hand, 1 randomized, placebo-controlled, double-blind study[37] of geriatric depression (N = 14) found that addition of vitamins B_1, B_2, and B_6 (pyridoxine) to a tricyclic antidepressant led to modestly better outcome when compared with placebo. Although the general public may assume that large doses of B vitamins are safe, peripheral neuropathy has been reported with "mega-doses" (> 500 mg/day) of pyridoxine in women self-medicating for premenstrual syndrome.[38]

Finally, although not widely promoted as "antidepressants," omega-3 fatty acids are under active investigation as mood-stabilizing agents in bipolar disorder, with some encouraging but very preliminary results.[39] Thus far, no significant neuropsychiatric complications of omega-3 fatty acids have been reported, but long-term efficacy and safety of large doses remain unknown.

DISCUSSION

It is difficult to find reliable figures on the number of Americans taking herbal and over-the-counter products for depression; a MEDLINE search (May 3, 2000) turned up no published studies. However, the *PDR for Herbal Medicines*[4] states that "sales of herbal remedies are doubling every 4 years," suggesting that this is a growing public health issue. While herbal and other over-the-counter depression remedies may generally be safe, and perhaps in some cases helpful, clinicians must be alert to covert use of these agents and their possible adverse psychiatric side effects. While the *PDR for Herbal Medicines* is a useful compendium of information, it should not be considered a definitive source on the prevalence of adverse neuropsychiatric effects of herbal remedies. The same applies to literature searches. First of all, since consumers often use herbal and over-the-counter agents without a physician's supervision, adverse reactions may never be observed or reported, much less published. Clinicians who do observe adverse reactions to herbal and over-the-counter agents may not be aware that the patient has been using these agents, or may not link the adverse reaction to the offending agent. Furthermore, there is no systematic reporting mechanism that would allow either manufacturers or the FDA to "keep track" of adverse reactions to herbal and over-the-counter agents. Finally, clinicians should always consider the possibility—as yet unexplored in systematic studies—that herbal remedies may interact with prescribed psychotropic medications.

Even though side effects from herbal agents are often mild, the induction of manic or psychotic symptoms has been associated with several over-the-counter agents, including St. John's wort, SAMe, and perhaps inositol. It is clear that while the general public often regards these remedies as safe "organic" alternatives to prescribed antidepressants, this conclusion is premature. Large-scale, controlled studies are clearly needed, and greater "oversight" responsibility on the part of the FDA now seems advisable. And while this article has not focused on studies of efficacy, this remains a critical issue for a very simple reason: severely depressed or suicidal individuals who self-medicate with herbal and over-the-counter agents may be risking their lives on largely untested agents. In the meantime, clinicians routinely should ask their patients if they are using any over-the-counter remedies and caution them about possible herb-drug interactions. While herbal and other alternative agents hold promise for some depressed patients, we must also be aware of their potential perils.[40,41]

Drug names: amitriptyline (Elavil and others), digoxin (Lanoxin and others), divalproex sodium (Depakote), haloperidol (Haldol and others), indinavir (Crixivan), nefazodone (Serzone), paroxetine (Paxil).

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