

by KAUSTUBH G. JOSHI, MD, CAPT, USAF, MC, FS; and MATTHEW D. FAUBION, MD, MAJ, USAF, MC

Dr. Joshi is a staff forensic psychiatrist at Wilford Hall Medical Center (US Air Force); and Dr. Faubion is the director of consult-liaison and forensic psychiatry services at Wilford Hall Medical Center (US Air Force) as well as a clinical assistant professor with the University of Texas Health Science Center of San Antonio.

# Mania and Psychosis Associated with St. John's Wort and Ginseng

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## ABSTRACT

The use of complimentary/alternative medicine has become popular as evidenced by grocery store aisles and “infomercials” devoted to herbal products. These products are often misconstrued as safe because of their natural origin. With an increase in the consumption of these products, physicians need to be aware of their potential adverse effects. There are several popular over-the-counter herbal products that can affect one’s behavior, especially resulting in acute mania and/or psychosis. This article provides an overview of existing literature regarding the increased use of herbal agents, reviews several case reports describing a potential association between herbal products (St. John’s Wort and ginseng) and the development of mania and psychosis, and discusses the limitations in determining the frequency of serious adverse effects due to herbal products.



St. John's Wort

## ADDRESS CORRESPONDENCE TO:

**Kaustubh G. Joshi, MD, Capt, USAF, MC, FS, Staff, Forensic Psychiatry, US Air Force  
59 MDOS/MMCU, 2200 Bergquist Ave. Ste. # 1, Lackland AFB, TX 78236  
Phone: (210) 292-4884; Fax: (210) 292-5944; E-mail: kaustubh.joshi@lackland.af.mil**

## INTRODUCTION

The purpose of this article is to review existing literature regarding the increased use of herbal agents, present several case reports describing a potential association between herbal products (St. John's Wort and ginseng) and the precipitation of mania and psychosis, and discuss the limitations in determining the frequency of serious adverse effects due to herbal products. Given the popularity of the complementary/alternative medicine industry, physicians should ask their patients if they are taking these products as they can have potential adverse side effects, such as extreme behavior changes. Physicians commonly concern themselves with the results of blood alcohol and urine toxicology screens to determine if an individual may have been under the influence of a substance that could have resulted in the patient's bizarre behavior. Many people believe herbal products are safer than prescribed medications due to their "natural" origin and over-the-counter status. Herbal products, often sold as supplements, can affect one's behavior.

## MAGNITUDE OF HERBAL THERAPY USE

Society's concern for its own health has increased as evidenced by a move toward a more health-conscious lifestyle. Many people use natural and organic therapies in lieu of prescription medications. In 1996, more than \$11 billion was spent on chiropractic, homeopathic, and herbal therapies,<sup>1</sup> and \$6.5 billion was spent exclusively on herbal medications in 1996 alone. This is a growing trend as there was a 380 percent increase in the use of herbal therapies from 1990 to 1997.<sup>2,3</sup> This increase in herbal product use is partly attributed to the perception of herbal remedies as "natural and safe." One in three Americans surveyed in 1997 admitted to using

an herbal preparation in the previous 12 months.<sup>3</sup> Although some people used herbal therapies exclusively (estimated to be 4.4% of those using herbal products), this is a small number compared to the 15 million Americans who used herbal medications in conjunction with prescription drugs in 1997.<sup>4</sup> The concomitant use of herbal therapies with prescription medications increases the possibility of herb-drug interactions, which can affect a patient's health.

Herbal products are widely available and found in most supermarkets and specialized health food stores. In the early 1990s, the profile of a typical herbal product user was a well-educated, employed, young, Caucasian female who adhered to a healthy lifestyle;<sup>5</sup> however, herbal product use has now spread across all ages, genders, and ethnicities. The most common uses for herbal therapies are headache, insomnia, anxiety, and back pain; these symptoms are also the most common presenting complaints to a family practitioner's office.<sup>4</sup> Certain subpopulations have shown more herbal product use than the general population (e.g., 16% of patients with irritable bowel syndrome, 20% of HIV-positive patients, 20% of organ transplant recipients, and up to 50% of those afflicted with Alzheimer's disease [most often dosed by their caregivers] use herbal therapies).<sup>6-11</sup> These medically ill individuals are also at a higher risk for developing herb-drug and drug-drug interactions as they are more likely to be on multiple prescription medications.

## HERBAL SAFETY AND REGULATION

Most people assume herbal products are safe because they are natural. There are several factors that influence the safety of herbal compounds, including regulation (or lack thereof), terminology, variable potency, and adulter-

ants. In the Dietary Supplement and Education Act (1994), the federal government addressed herbal products and placed them in the same regulatory category as vitamins and minerals. This legislation allowed companies to market herbal preparations without prior proof of efficacy. Some proof of safety is required but no specific documentation is required prior to sale in the United States. Specific therapeutic claims are not allowed, but a company can make general statements about the herbal product's impact on the body. For instance, the manufacturer cannot claim the herbal product improves memory, but can claim that it improves the mind. A similar claim can be made about enhancing physical performance.

Another potential area of concern deals with terminology. Often, the same name describes different herbals. Fang-ji usually refers to *Stephania tetrandra* or *Cocculus trilobus*, which are benign compounds. In Hong Kong, Fang-ji refers to *Aristolochia fangchi*, which is a nephrotoxic species.

There is considerable variation in the amount of active ingredients in the herbal preparation. Where the herb was cultivated, when the herb was harvested, and how the herb was stored all impact the potency of the preparation.<sup>5</sup> These variables are difficult to control and make standardization of herbal preparations problematic. In addition to the variable amounts of active compound in an herbal preparation, there are adulterants in these products. Adulterants are particularly prevalent in herbal products from India and China.<sup>5</sup> Steroids, benzodiazepines (e.g. diazepam), diuretics, heavy metals, hormones (particularly thyroid hormone), tranquilizers, anti-inflammatories, and antihistamines are common adulterants in herbal products.<sup>5</sup>

Herbal products can have side

effects, such as nausea, diarrhea, and skin rash (which can be due to the active product and/or the adulterant); they can also have more serious side effects.<sup>12,13</sup> Ginseng has been implicated in hypertensive emergencies and chamomile teas have been reported to cause anaphylactic reactions.<sup>14,15</sup> Ma-huang (banned by the U.S. Food and Drug Administration [FDA] in 2004) has caused anticholinergic delirium in young party-goers.<sup>2,5</sup>

St. John's Wort and ginseng have been top-ten selling herbal products over the past decade.<sup>2-5</sup> A MEDLINE search of case reports over the past 25 years of mania and/or psychosis associated with these two products was done to illustrate the potential of herbal products to result in behavior changes. It is quite possible that there are other herbal products that can result in mania and/or psychosis, but St. John's Wort and ginseng were selected based on consumer popularity.

## ST. JOHN'S WORT

Antidepressants can precipitate mania in a predisposed individual.<sup>16</sup> On average, 8 to 10 years pass between an individual's first symptoms and an ultimate diagnosis of Bipolar I Disorder.<sup>17</sup> Up to 25 percent of patients presenting with depression will be diagnosed with Bipolar I Disorder.<sup>18</sup> Manufacturers tout St. John's Wort (marketed as an antidepressant and available over-the-counter) to assist with mood, energy, concentration, stress relief, and a sense of well-being.

Ancient Greek physicians used St. John's Wort (*Hypericum perforatum*) for headaches, stomachaches, and a plethora of other ailments. It is ranked in the top five for sales of dietary supplements in the United States and widely used for its antidepressant effect in the US with sales in excess of \$200 million in 1997. The active ingredients in St.

John's Wort are hypericin and pseudohypericin with a plasma half-life of 24 hours. It has an effect on the central nervous system as evidenced by an affinity for a variety of neurotransmitters including GABA-A, GABA-B, serotonin, MAO-A, and MAO-B.<sup>1,20</sup> One study showed a 50-percent increase in 5-HT1A and 5-HT2A receptors after six months of use.<sup>21</sup> St. John's Wort has also been shown to cause non-specific EEG changes.<sup>22,23</sup> Several studies have shown that St. John's Wort inhibits cytochrome 3A4 acutely and then induces this enzyme with repeated administration; other authors have reported possible *in-vivo* and *in-vitro* inhibition of cytochromes 2C9 and 2D6.<sup>24-26</sup> St. John's Wort can significantly increase or decrease blood levels of many prescribed medications that are cleared by the cytochrome P450 pathway. Examples of medications with altered clinical effects or drug concentrations with concomitant use of St. John's Wort include oral contraceptives, simvastatin, and warfarin.<sup>27</sup> Although there is a wide receptor-binding profile, the exact mechanism of action is unknown.

Common adverse effects include gastrointestinal symptoms, skin reactions, fatigue and sedation, restlessness, dizziness, headache, and dry mouth.<sup>27</sup> Several recent meta-analyses, a clinical trial, and an observational trial have concluded that the rates of adverse effects of St. John's Wort are about 1 to 3 percent, which is comparable to those of placebo and less than that of standard antidepressant treatment.<sup>27</sup> None of these meta-analyses gave a frequency of each specific adverse effect.

**Case Report 1.** A 20 year-old male without a prior psychiatric history (an uncle had been diagnosed with Bipolar I Disorder) consumed St. John's Wort at a dosage of 300mg orally t.i.d. (man-

ufacturer's recommended daily dose) for three days prior to presentation.<sup>28</sup> After three days of use, he became irritable, had increased energy, and a decreased need for sleep. He also developed psychotic symptoms to include ideas of reference with respect to a pet cat. He was treated as an outpatient with lithium carbonate. These symptoms persisted for seven days following discontinuation of the St. John's Wort. Eventually the patient was diagnosed with Bipolar I Disorder and was maintained on lithium carbonate despite ceasing St. John's Wort use.

**Case Report 2.** A 51-year-old woman with a 25-year history of stable Bipolar I Disorder was treated with haloperidol and lithium for fifteen years and was in remission for the past 10 years without psychotropic medications.<sup>28</sup> She consumed St. John's Wort (dose of 300mg t.i.d.) to cope with a mild, stress-related depressed mood for two weeks prior to presentation. She developed pressured speech, experienced auditory hallucinations, and became hypersexual. She was admitted to the hospital for seven days during which her lithium was restarted. She required lithium maintenance despite ceasing use of St. John's Wort.

**Case Report 3.** A 26-year-old woman with schizophrenia remained well for three years without perphenazine treatment following complete remission.<sup>29</sup> Five months before her relapse, she used St. John's Wort in her tea once or twice a week, which she increased to daily two months before relapse. She became acutely psychotic with paranoid delusions, ideas of reference, and loosening of associations. Her psychosis responded to olanzapine.

**Case Report 4.** Another case involves a man treated for new onset psychosis at age 34 with risperidone, which his psychiatrist stopped after being symptom free

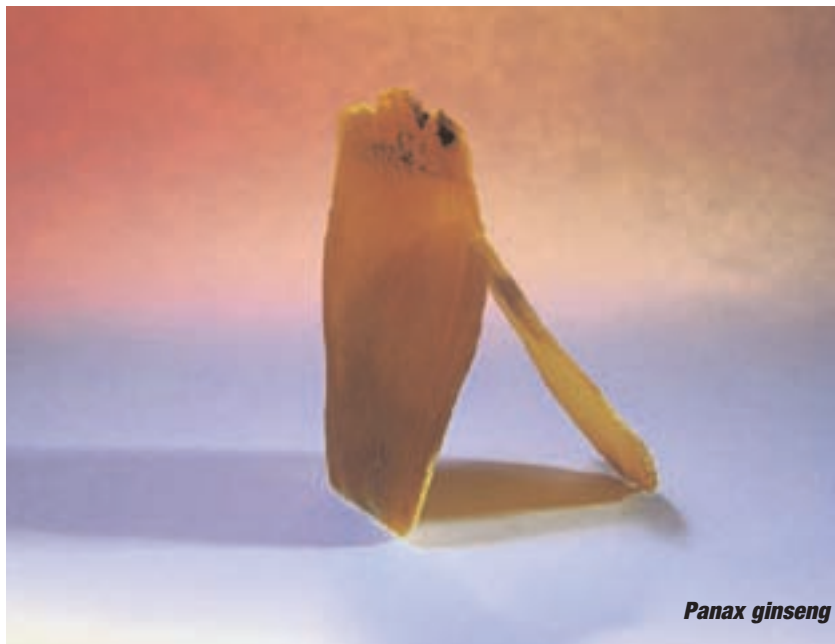
for one year.<sup>29</sup> He remained well for seven months without medication when he had an abrupt recurrence of persecutory delusions, ideas of reference, and bizarre behavior over a two-week period. His psychotic episode again responded to risperidone. The patient purchased St. John's Wort two to three months prior to relapse and was consuming it daily (it is unclear from the case report how much St. John's Wort he was consuming).

## GINSENG

Ginseng (genus *Panax*) is a popular "tonic" herb, which when taken regularly has cumulative strengthening effects.<sup>30</sup> There are several varieties of ginseng: *Panax ginseng* (grown in north-eastern China and Korea), *Panax quinquefolius* (grown in the United States and Canada), and *Panax notoginseng* (grown in southwest China). "Siberian ginseng" (*Eleutherooccus senticosus Maxim*) is not ginseng.

Ginseng is marketed to relieve stress and fatigue and improve endurance.<sup>1</sup> The side effects are relatively rare, occurring with consuming high doses and/or use over long periods of time; these include insomnia, nervousness, diarrhea, and hypertonicity.<sup>31,32</sup> Although several mechanisms of action have been postulated, it most likely affects the hypothalamic-pituitary-adrenal axis, resulting in elevated corticotropin and corticosteroid levels.<sup>1,33,34</sup> There are case reports of herb-drug interactions with phenelzine and warfarin.<sup>35</sup> There are no consistent case reports of ginseng altering the cytochrome P450 pathway. The World Health Organization (WHO) reported four cases of mania and psychosis from ginseng monopreparations and four cases from ginseng combinations worldwide from its database in 2002.<sup>35</sup>

**Case Reports.** A 26-year-old man with a suicide gesture at age



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16 after a relationship breakup (requiring no medication and only two counselor visits) was brought to the hospital by a friend following two months of increasingly bizarre behavior.<sup>32</sup> For two months prior to presentation, he consumed Chinese ginseng five days a week to boost his energy. While taking ginseng, he became increasingly restless, needed few hours of sleep, and felt energetic. A month before presentation, he had racing thoughts and became preoccupied with work, finances, and his family. On the day of admission, he was grossly disorganized, circumstantial, grandiose, and agitated. He was started on valproic acid; 10 days

after his admission, his symptoms began to markedly improve. His wife reported that he took the equivalent dose of 250mg ginseng root per day, which was consistent with the manufacturer's recommendations. He was eventually tapered off the valproic acid with no return of symptoms.

In another case, a woman with a history of depressive episodes maintained on amitriptyline and lithium carbonate became manic 10 days after discontinuing her regular medications and starting a daily regimen of ginseng.<sup>36</sup> In two other cases, concurrent use of phenelzine with ginseng was associated with manic-like episodes.<sup>37,38</sup>



## DISCUSSION

Despite case reports of mania and/or psychosis associated with herbal use, it is difficult to determine the frequency of these particular adverse effects due solely to herbal products. The broad biochemical and pharmacological actions are not fully understood, resulting in speculation as to which transmitters and/or receptors result in altered behavior. Many patients take prescribed medications in addition to herbal products; they could also consume herbal products in higher dosages than recommended by the manufacturer. Herbal products can alter hepatic microsomal enzymes, which can affect the half-life of medications. In turn, prescribed

Another obstacle in determining the frequency of manic and/or psychotic symptoms as adverse effects is that underreporting prohibits a calculation of their true incidence. A recent report from the Office of the Inspector General of the U.S. Department of Health and Human Services concluded that current surveillance systems for identifying adverse reactions from dietary supplements probably detect less than one percent of all adverse reactions.<sup>41</sup> Among the factors that may contribute to underreporting are that many consumers presume these products to be safe, use these products without the supervision of a healthcare professional, and maybe unaware that the FDA

information and adequate reporting of adverse events, it is difficult to track the frequency of serious adverse effects such as mania and psychosis occurring from herbal product use.

## CONCLUSION

Complementary/alternative medicine is a popular phenomenon. These compounds are marketed as safe, natural alternatives to prescription medication. As their use increases, it is highly possible that the incidence of potential adverse side effects could increase as well—including mania and psychosis. The cases presented above do not establish a cause-effect relationship. Although by no means definitive,

# Maintaining a supportive and nonaccusatory stance with the patient will foster a therapeutic alliance to facilitate discussion of potential risks of continued herbal product use.

medications can induce microsomal enzymes, which can lead to hepatotoxicity of various herbal products. These potential herb-drug interactions can cause potential adverse effects. Infants, children, and elderly are more vulnerable to adverse reactions because of their tendency to build up higher drug levels and concomitant decreased ability to metabolize active agents, unlike healthy young adults who often possess the physiologic capacity to properly metabolize herbal medicines with only limited reactions.<sup>39,40</sup> Herbal products can induce patients with a pre-existing psychiatric illness and/or intervening medical conditions into a manic episode and/or psychotic relapse. Caffeine, alcohol, and illicit substance use can increase susceptibility to potential adverse effects from herbal products.

regulates them.<sup>41</sup> The FDA lacks much of the information to analyze adverse event reports due to limited medical information, limited product information, limited manufacturer information, and lack of adverse events reports being reported; the FDA had to shut down its central database website “Special Nutritionals Adverse Event Monitoring System” on August 29, 2002, due to limited data.<sup>42</sup> The World Health Organization Collaborating Center for International Drug Monitoring Database tracks adverse events associated with allopathic and herbal products from national drug safety bodies from 18 countries; since it relies on member nations to submit reports, it experiences similar problems as the FDA in terms ensuring completeness and accuracy of reports.<sup>35</sup> Without a central repository of

these cases raise the possibility that herbal products are associated with potential adverse effects such as mania and psychosis. With limited data, unclear mechanisms of actions, herb-drug interactions, and a possible underlying mental illness, it is difficult to estimate the true prevalence of mania and psychosis associated with herbal products alone. Mania and psychosis can impair judgment, which can result in engagement in reckless activities that can result in harm to oneself and/or others. Given the severity of these conditions, it is important to look at all causes, including herbal product use. Primary care and mental healthcare providers should consider inquiring about herbal product use during initial and follow-up assessments. Maintaining a supportive and nonaccusatory stance with the patient will foster

a therapeutic alliance to facilitate discussion of potential risks of continued herbal product use.

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