

Herbal Products and Other Supplements: Use by Elderly Veterans With Depression and Dementia and Their Caregivers

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ABSTRACT

The use of herbal products and other “natural” supplements among the US population is on the rise. Limited data suggest that such use among the elderly may correlate with higher education levels as well as psychiatric symptoms. The authors examined herbal/supplement use among elderly veterans with depression and/or dementia (n = 82) and their primarily elderly caregivers (n = 56). Eighteen percent of subjects and 16% of caregivers used herbals/supplements. Seventy-five percent of subjects who used these products during the study period were also taking potentially interacting medications. Given the prior association of herbal/supplement use with higher education levels, a surprising number of elderly veterans with depression and/or dementia (the majority of whom had high school or less education) used these products. As evidenced by missing documentation in many physician notes, subjects may not have discussed their usage of herbals/supplements with their physicians. In light of the possibility of potentially harmful drug interactions, physicians who treat elderly patients should regularly inquire about the use of these products. (*J Geriatr Psychiatry Neurol* 2004; 17:25–31)

Keywords: elderly; alternative medicine; dementia; depression

Use of herbal alternative medicine in the US population is on the rise. Eisenberg’s landmark study found that herbals were used by 3% of Americans in 1991; by 1997, this rate had increased to 12%.¹ The most recent large-scale survey of mixed-aged community adults found that herbal products and other “natural” supplements were being used by 14% of those surveyed, of whom 16% were also prescription drug users and 22% were fluoxetine users.² In

mixed-age samples, various correlates of alternative medicine use reported include higher education level, psychiatric illness or symptoms, poorer health status, holistic orientation, female gender, and affluence.³

There are limited data on use of herbals/supplements among the elderly. While Busto et al⁴ found that 5% of Canadian community elderly used herbal products as hypnotics and Foster et al⁵ found that 8% of older adults surveyed used herbals, Astin et al⁶ reported a much higher rate of herbal use, 24%, among their study population of California Medicare enrollees. In the latter study, herbal use significantly correlated with education, depression and anxiety, and younger age. Notably, the education level of the Astin et al sample was high: 75% had at least some college education, and 15% had graduate degrees; among users of herbals/supplements, 53% had graduate degrees.

Two studies have examined use of herbals/supplements in patients with cognitive complaints. Coleman et al surveyed caregivers of patients with Alzheimer’s disease (AD) and found that 11% of patients had tried herbal preparations and 9% had tried dietary supplements touted as “smart pills.”⁷ No patients had taken these alternative therapies for behavioral problems; use was largely confined to the first 2 years of illness and did not correlate with any caregiver characteristics. Another study in a dementia

Received April 1, 2003. Received revised September 9, 2003. Accepted for publication September 16, 2003.

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This article was presented at the AAGP 15th Annual Meeting, Orlando, Florida, 2002. This research was supported by a University of Michigan Geriatrics Center/Institute of Gerontology Pilot Grant, the Rachel Upjohn Scholars Program at the University of Michigan, and a Health Services Research and Development Research Career Development Award from the Department of Veterans Affairs.

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DOI: 10.177/0891988703261998

clinic surveyed caregivers about referred patients (none of whom actually had dementia); herbals/supplements were being used by 10% of these patients.⁸ In terms of depression or depression in dementia, there do not appear to be any elder-specific studies to date.

As is well known to physicians (but not to many consumers), producers of herbals/supplements are not required to submit proof of safety and efficacy to the US Food and Drug Administration prior to marketing. In addition, physicians are often not informed of the use of herbals/supplements by their patients.¹ As such, the adverse effects and drug interactions of these preparations are discovered empirically as patients take these substances in combination with other medications. Reports of drug interactions have included ginkgo and antiplatelet agents,⁹⁻¹⁰ ginkgo and trazodone,¹¹ St John's wort and serotonin reuptake inhibitors,¹² St John's wort and warfarin,¹³ St John's wort and cyclosporin,¹⁴ St John's wort and digoxin,¹⁵ ginseng and monoamine oxidase inhibitors,¹⁶ and ginseng and warfarin.¹⁷ Drug interactions are a particular concern in the elderly, many of whom are taking multiple prescription and nonprescription medications. Late-life depression and dementia are frequently associated with other comorbid illnesses;¹⁸ as such, drug interactions are an additional serious concern in elderly patients with depression and/or dementia.

Given the limited information regarding use of herbals/supplements among elderly patients with depression and/or dementia, the purpose of this study was to provide a preliminary estimate of herbal/supplement use as part of a larger study on outcomes in elderly veterans with depression and/or dementia. Use of herbals/supplements in younger adults has correlated with factors including female gender, affluence, and higher education levels. As we decided to study this issue in an elderly veteran population (mostly men with lower mean socioeconomic status and education levels than the Astin study⁶), we hypothesized that the use of herbals/supplements would be significantly lower than that found in the latter study (24%) and likely lower than the rates found in previous community studies. In light of recent findings of drug interactions and potential side effects with herbals/supplements, we thought it was important to have a preliminary estimate of use of herbals/supplements among veterans who may have poorer health status and more medical conditions than nonveteran patient populations, related in part to the older age of veteran patients.¹⁹ We also sought to examine to what extent the caregivers of these patients themselves might be using herbals/supplements.

METHODS

This study was conducted as part of a larger project, a 1-year observational study comparing outcomes among elderly

subjects with depression, dementia, and coexisting dementia and depression. Another part of the project examined outcomes among caregivers of these groups of subjects. Questions regarding use of herbals/supplements were included as part of the overall project questionnaire.

Subjects were recruited from inpatient (medical/surgical and psychiatric units) and outpatient (both primary and specialty clinics) settings at the Veterans Affairs (VA) Ann Arbor Healthcare System between 1998 and 2000 and screened using the Geriatric Depression Scale (GDS)²⁰ and the Mini-Mental State Exam (MMSE).²¹ Individuals scoring either greater than 5 on the GDS and/or less than 23 on the MMSE who were willing to participate then completed written informed consent procedures after a description of the study and its risks and benefits. If a subject's competence was in doubt, consent was obtained from, in order of legal priority, the legally appointed guardian, power of attorney, spouse, adult son or daughter, or adult sibling.

Following informed consent, individuals with positive screens had a diagnostic interview with a board-certified geriatric psychiatrist (H.C.K.) as well as review of the VA's electronic chart for further history, laboratory studies, and so forth. Dementia diagnoses were made using National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA)²² criteria for probable or possible AD and National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS/AIREN)²³ criteria for probable or possible vascular dementia. *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (*DSM-IV*),²⁴ criteria were used to make the diagnosis of depression. In the case of making the diagnosis of depression in subjects with dementia, "overlap" symptoms (such as weight loss that could be common either to depression or dementia) were included as depressive symptoms when they had been present for at least 2 weeks and represented an acute change from previous function (eg, over several weeks' time). Following this interview process, subjects diagnosed with probable major depression, dementia (either AD or vascular), or depression in dementia were invited to participate in the study. Individuals who did not meet criteria for dementia or depression were excluded from further study at that point. Many of the included subjects had caregivers who either helped direct or did direct the subject's health care; these caregivers were also invited to participate in the caregiver arm of the study.

A total of 215 patients recruited or referred to the study were screened for depression and dementia. Of these, 123 had positive screens for depression and/or dementia and were invited to complete the diagnostic interview. Fourteen patients with positive screens declined further participa-

tion; 27 of the remaining 109 potential subjects were excluded following diagnostic interview as they did not meet criteria for major depression and/or dementia or had cognitive impairment due to other causes (B12 deficiency, Parkinson's disease, etc). In most cases, dementia and depression as determined by study interview had been diagnosed prior to the study by treating/nonstudy physicians (97% of subjects with dementia and 86% of subjects with depression). The final sample included 27 subjects with major depression, 26 subjects with dementia, and 29 subjects with depression/dementia. For the purposes of the herbal/supplement survey, these patients were added together to comprise the subject group ($n = 82$). Of the entire subject group, 56 patients had caregivers who comprised the caregiver group.

Use of herbals/supplements was defined as use of either herbal products (ginkgo biloba, St John's wort, etc) or other "natural" supplements (melatonin, glucosamine, etc). As part of the larger study survey, subjects and participating caregivers were asked, "Have you ever taken any 'natural,' 'alternative,' or herbal (ginkgo, St John's wort) treatments, supplements, or any items from a health food store?" Those responding affirmatively were questioned further regarding details of usage (types of herbals/supplements, time frame of past/current usage). In subjects with dementia, caregiver corroboration regarding both the subject's use of herbals/supplements as well as other medications was obtained.

In addition to the above information, subjects' medication lists were obtained from 2 sources: (1) the subject's personal medication list and (2) the VA's computerized pharmacy data. Specific medications of interest included those with potential interactions with herbals/supplements (eg, ginkgo biloba and aspirin, St John's wort and digoxin, psychotropics or medications with psychoactive properties). At study intake, total medical illness burden was assessed via the Cumulative Illness Rating Scale (CIRS).²⁵ Caregivers' use of insomnia treatments was also collected.

Categorical differences were assessed using chi-square tests of independence, and continuous variables were compared by analysis of variance (ANOVA). Tukey's HSD procedure was used to test post-hoc differences between diagnostic groups. A criterion alpha level of .05 was used throughout. Spearman correlation coefficients were employed to examine the strength of the relationship between use of herbals/supplements and variables including those potentially affecting such use based on prior studies. For subjects, the latter included marital status, education level, MMSE score (level of cognition), CIRS score (total medical illness burden), GDS score (depression severity), and treatment of depression by the subject's treating physician. For caregivers, variables included in the herbal/supplement correlation analysis included age, gender, education level, self-rated health status, self-reported psychiatric symptoms, and level of caregiver burden.

RESULTS

A total of 82 subjects with dementia and/or depression and a total of 56 caregivers were studied. The mean age of subjects was 79.1 years. All subjects were male. The majority of subjects (76%, $n = 62$) were Caucasian, with 16% African American, 6% Hispanic, and 2% other races/ethnicities. Notably, 76% ($n = 62$) of subjects had an education level of high school or less. Sixty-three percent ($n = 52$) of subjects were married, and 68% ($n = 56$) of subjects had caregivers. Mean and range screening test scores for the entire ($n = 82$) subject group were mean MMSE = 19.5, range = 0-30; mean GDS = 6.6, range 0-15; and mean CIRS = 9.2, range = 2-21.

Among the study subgroups, there were no significant demographic differences except for mean age. Age was significantly higher in subjects with dementia alone (81.7 years) or coexisting dementia and depression (80.8 years) than in subjects with depression alone (74.5 years; $F = 11.61$, $df = 2, 79$, $P < .0001$). For the subject subgroups, mean screening test scores were mean MMSE for depression-alone subjects = 26.6, for dementia-alone subjects = 16.6, for depression/dementia subjects = 15.2; mean GDS for depression-alone subjects = 9.7, for dementia-alone subjects = 2.7, for depression/dementia subjects = 6.9; and mean CIRS for depression-alone subjects = 11.3, for dementia-alone subjects = 8.5, and for depression/dementia subjects = 10.3. Subjects with depression alone had significantly higher levels of medical burden as reflected on mean CIRS score than subjects with dementia alone ($F = 3.74$, $df = 2, 79$, $P < .03$).

Among herbal/supplement users, mean age was 76.2 years. Eighty percent ($n = 12$) of herbal/supplement users were Caucasian, and 60% ($n = 9$) had a high school education or less. Eighty-seven percent ($n = 13$) of herbal/supplement users were married, and 53% ($n = 8$) had caregivers. Mean and range screening test scores for the herbal/supplement users ($n = 15$) were as follows: mean MMSE = 22.9, range = 4-29; mean GDS = 6.7, range = 0-15; and mean CIRS = 9.5, range = 4-16. Further analyses were performed to test for significant demographic or test score differences between the herbal/supplement group and the remainder of the overall subject group ($n = 67$). Herbal/supplement users were significantly more likely to be married than those who did not use herbals/supplements (54%, $n = 36$; $\chi^2 = 5.53$, $df = 1$, $P < .02$). Herbal/supplement users were also younger, had more education, and had a higher mean MMSE score than nonusers (mean age = 79.7, 82% [$n = 55$] with high school education or less, and mean MMSE = 19.0), but these differences were significant at trend levels only (0.06, 0.07, and 0.098, respectively).

The majority of caregivers (71%, $n = 40$) were elderly female spouses of subjects. The mean age of caregivers was 67 years. Eighty-two percent ($n = 46$) were Caucasian, 16% were African American, and 2% were Hispanic.

Table 1. Subjects and Caregivers Who Used Herbals and Supplements

<i>Subject/ Caregiver</i>	<i>Diagnosis</i>	<i>Herbal/ Supplement</i>	<i>Time of Use</i>	<i>Concurrent Psychotropics/Psychoactives or Potential Drug Interactions</i>
Subject				
1	DEP	Ginkgo biloba, ginseng	Baseline through 12 months	Aspirin, ibuprofen, phenytoin, oxazepam, digoxin, lamotrigine
2	DEP	St John's wort	Baseline through 12 months	Mirtazepine, oxazepam (B-6 months), alprazolam, clonazepam, zolpidem (month 12)
3	CDD/AD	Ginger root	Baseline	Carbamazepine, gabapentin, sertraline, risperidone, Tylenol with codeine, aspirin
4	DEM/AD	Ginkgo biloba	Year prior to study	
5	CDD/VD	St John's wort	Year prior to study and 6 months	Nefazodone, trazodone, valproic acid (month 6)
6	CDD/AD	Ginkgo biloba	Baseline	Aspirin, paroxetine, haloperidol, oxazepam
7	DEP	St John's wort	Year prior to study	
8	DEM/VD	Ginkgo biloba	Prior to study	
		"Doctor Whitaker's"	Baseline through 12 months	
		Ginseng	Months 3-12	
		Lutein	Months 6-12	
		Bilberry	Months 6-12	
		"MSM"	Month 12	
9	DEM/AD	Ginkgo biloba	Baseline through 12 months	Phenytoin
		Saw palmetto	Month 6	
		Ginseng	Month 6	
10	DEP	"Reliv" supplement	Baseline through 12 months	Sertraline, aspirin
11	DEM/AD	Ginkgo biloba	Three years prior to study	
		Echinacea	Baseline	
12	DEP	Ginseng	Baseline	Digoxin, paroxetine
13	DEP	St John's wort	Year prior to study	
14	DEP	Ginkgo biloba	Year prior, months 6-12	
15	CDD/AD	"GH3" supplement	Baseline	Naproxen, lorazepam, Tylenol with codeine
		"Arthro-Z" supplement	Months 3-12	
Caregiver				
1		St John's wort	Baseline, 6 months, 12 months	
2		Ginkgo biloba	Baseline to 3 months	"Tylenol PM" (baseline)
		Uva ursi	3 months	Alprazolam (month 3)
3		Ginkgo biloba	Baseline	
4		"Reliv" supplement	Baseline through 12 months	
5		Ginkgo biloba	Baseline	
		Melatonin	Baseline	
6		Valerian root	Baseline	Antihistamine for sleep
		Melatonin	Baseline	
		Glucosamine/ chondroitin	3 months	
7		"MSM"	Baseline	
8		Arnica	Baseline	
		Evening primrose	3 months	
		Melatonin	3 months	
9		Cod liver oil	Baseline	"Tylenol PM" (baseline)

Note: DEP = major depression; DEM/AD = Alzheimer's dementia; DEM/VD = vascular dementia; CDD/AD = coexisting major depression and Alzheimer's dementia; CDD/VD = coexisting major depression and vascular dementia.

Subject Use of Herbs/Supplements

Eighteen percent ($n = 15$) of subjects had recent (in the past several years) or current herbal/supplement use. Use of herbals/supplements by these subjects is detailed in Table 1.

Twelve percent ($n = 10$) of subjects were using herbals/supplements at intake into the study. Over the 12-month study period, 15% ($n = 12$) of the subjects used herbals/supplements. The single most commonly used herbal/supplement, taken by 47% of subjects using herbals/supplements, was ginkgo biloba; the majority of ginkgo users (71%) had dementia (alone or coexisting with depression). The next most commonly used herbal/supplement was St John's wort, taken by 27% of subjects who used herbals/supplements; all users of St John's wort had depression (alone or coexisting with dementia). Other

herbals/supplements used less commonly included ginseng, echinacea, ginger root, "Reliv" supplement, saw palmetto, and GH3. Only 2 subjects using herbals/supplements also had a caregiver who was using herbals/supplements.

Caregiver Use of Herbs/Supplements

Sixteen percent of caregivers ($n = 9$) were using herbals/supplements; use of herbals/supplements by these caregivers is also listed in Table 1. As above, only 2 of these caregivers took care of a subject who was also using herbals/supplements. Of caregivers using herbals/supplements, 88.9% ($n = 8$) were the female elderly spouses or significant others of subjects. The most commonly used herbals/supplements were ginkgo biloba and melatonin, each taken by 33% of caregivers using

herbals/supplements. Use of herbals/supplements in caregivers was notable for usage of a variety of less common herbals/supplements including uva ursi, valerian, and evening primrose. Forty-four percent ($n = 4$) of caregivers taking herbals/supplements suffered the death of the subject (spouse, $n = 3$, or father, $n = 1$) during the study period.

Correlations With Subject and Caregiver Use of Herbals/Supplements

Additional analyses were performed to examine the correlation of various subject and caregiver variables with use of herbals/supplements. Use of herbals/supplements in subjects correlated with marital status (being married: correlation coefficient = 0.25965, $P < .02$) but did not correlate with any of the other variables examined including education level, severity of medical illness burden, level of cognition (MMSE score), depression severity (GDS score), or treatment of depression. Herbal/supplement use in caregivers did not correlate with any of the variables examined, which included age, gender, education level, self-rated health status, self-reported psychiatric symptoms, and level of caregiver burden.

Potential Herb-Drug Interactions During the Study Period

Concomitant use of prescription or nonprescription medications with the potential to interact with herbals/supplements taken by subjects and caregivers during the study period is noted in Table 1. Of subjects using herbals/supplements during the actual study period, 75% ($n = 9$) took either concurrent psychotropics (selective serotonin reuptake inhibitors, trazodone, etc), psychoactive agents (codeine), or other drugs (digoxin, aspirin, etc) that could potentially interact with the herbal/supplement (though no such interactions were reported). Thirty-three percent ($n = 3$) of caregivers using herbals/supplements also took concurrent medications for insomnia.

Seventy-five percent ($n = 42$) of the overall subject group with depression were taking conventional antidepressants, while a lower percentage, 55% ($n = 6$), of depressed users of herbals/supplements were taking conventional antidepressants. Only 1 subject (subject 2) took St John's wort concurrent with a conventional antidepressant (undocumented in his psychiatrist's notes). This subject with refractory depression thought the herbal treatment might help where the prescription medications had not.

While 33% ($n = 18$) of the overall subject group with dementia were taking cholinesterase inhibitors, none of the subjects with dementia using herbals/supplements were taking cholinesterase inhibitors concurrently. Of subjects with dementia using herbals/supplements, 2 subjects (subjects 6 and 9) had tried cholinesterase inhibitors prior to the study, and 1 subject (subject 4) took donepezil after stopping ginkgo during the study period.

Physician Documentation of Herbal/Supplement Use

Treating/nonstudy physician notes contemporaneous with herbal/supplement use were available for 13 of the 15 subjects. Review of these notes revealed that physicians mentioned subjects' herbal/supplement use in 46% ($n = 6$) of subjects in at least 1 chart note. In the remaining 7 subjects, no mention was made of subject's use of herbals/supplements either in the text or medication list portions of the physicians' notes. Only 2 (15%) of the physician notes documented a discussion of potential interactions of herbals with prescribed medications.

DISCUSSION

Use of herbals/supplements was found in 18% of elderly veteran subjects with depression and/or dementia and in 16% of their caregivers. Ginkgo biloba was the single most commonly used herbal/supplement in both subjects and their caregivers. Subject use of herbals/supplements correlated only with marital status, and caregiver use of herbals/supplements did not correlate with any of the examined variables; the ability to detect significant correlations was likely limited by the small sample size. Herbal/supplement users were significantly more likely to be married than those who did not use these products. Users of herbals/supplements were also younger, had more education, and had a higher mean MMSE than did nonusers; however, these differences were significant at a trend level only. Of notable concern, a majority (75%) of the subject group using herbals/supplements during the study period were taking concurrent psychotropic, psychoactive, or other medications with the potential to interact with these substances, and many subjects' herbal/supplement use was not documented in contemporaneous treating physician notes.

We were surprised by the extent of use of herbals/supplements in our elderly veteran sample. Prior research has suggested that a strong correlate of herbal alternative medicine usage is level of education; in the Astin et al study, for example, 53% of those using herbal alternative medicine had graduate degrees, whereas only 25% had high school or less education.⁶ While the education level of subjects using herbals/supplements in our sample was higher than that of nonusers, it was still markedly lower than the Astin et al sample; 60% of our subjects using herbal/supplements had high school or less education.

Alternative medicine use may be higher in patients with certain diseases such as arthritis or psychiatric illness.³ We speculate that use of herbals/supplements may also be higher in the elderly with neuropsychiatric symptoms or syndromes such as dementia or late-life depression. We did not record the specific reasons for which subjects were using herbals/supplements. The majority were taking either ginkgo or St John's wort; presumably,

these products were taken to enhance cognition or to reduce depressed mood respectively. Many users of herbals/supplements with depression and/or dementia were not treated with either conventional antidepressants or cholinesterase inhibitors. Thus, use of ginkgo or St John's wort in some of these subjects may have been inversely related to whether subjects were willing to take (considering side effects or perceived efficacy) or physicians willing to prescribe (considering type or stage of dementia or nondetection of depression) "conventional" treatments. Other subjects may have sought to take some personal control over their illnesses by their use of herbals/supplements. Given that the marital status of subjects was found to be significantly correlated with herbal/supplement use, it is also possible that some of the spouses may have influenced subjects' decisions to use herbals/supplements. Further in-depth study of the reasons for herbal/supplement use in the elderly are needed.

The finding that 75% of elderly subjects using herbals/supplements during the study period were taking potentially interacting medications is particularly concerning. Of additional concern is the fact that many of these subjects may not have disclosed their use of herbals/supplements to their physicians, perhaps viewing such use as "safe" and "natural" or out of worry that their physician would view such use negatively. Thus, there is a potential for serious drug interactions such as potentiation of antiplatelet drugs with ginkgo biloba^{9,10} and induction of the P450 system with St John's wort,²⁶ interactions that could occur unbeknownst to the physicians caring for these patients.

Limitations of our study include the relatively small sample size and the focus on a male veteran subject population. The former may have affected the ability to correlate herbal/supplement use with factors such as education level, age, level of cognition, or depression severity. The latter may limit the study's generalizability to general clinic populations. In addition, subjects diagnosed as part of the larger study with depression and/or dementia were examined as a group; a larger sample would have enabled us to make comparisons between subgroups of subjects. As in prior studies examining use of herbals/supplements, this study describes use as reported by subjects and not actual use. Examining actual use during home interviews would have been optimal but was not possible given the distances many subjects lived from the hospital. We suspect, however, that actual use would have been even higher than reported use. Finally, subject recruitment for this study began in 1998, and final 1-year follow-up interviews were completed in 2001; given the time frame of the study, it is possible that use of specific herbals/supplements to enhance memory and mood (eg, ginkgo and St John's wort) may have changed as mixed or negative trial data emerged. These limitations notwithstanding, this study contributes to our

knowledge of the use of herbals/supplements in older patients, especially given the frequency that patients with mood/cognitive complaints are seen by practitioners who treat elderly patients.

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