ALTERNATIVE MEDICINE ALERT®

The Clinician's Evidence-Based Guide to Complementary Therapies

Thomson American Health Consultants Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Antioxidant Use During Chemo- and Radiotherapy for Cancer

By Howell Sasser, PhD

A DIAGNOSIS OF CANCER IS A LIFE-CHANGING EVENT. MANY NEWLY diagnosed patients who have not previously devoted much attention to their health now begin to show an intense desire to learn about the disease and potential treatments. This often includes changes in diet, exercise, stress reduction, and other lifestyle factors. Conversely, those who already took an active approach to health management before diagnosis may be concerned about what practices to modify or stop during cancer therapy. In both cases, it is important for the physician to be able to offer reliable advice and reassurance.

One such area of advice that has been controversial is the use of antioxidant supplements during adjuvant chemotherapy and radiation therapy. Use of vitamins A, C, and E, and beta-carotene for a variety of indications is very popular. Among the health benefits proposed for such agents are improved capacity for healing and immune system function, both of which would appear attractive for cancer patients. However, there is also at least an intuitive case why such agents should not be used. This article reviews recent published evidence for and against use of antioxidants during adjuvant therapies for cancer. Much of the difference in findings appears to arise from differences in definitions and procedures, such as dose and timing of administration. Also, few clinical studies have been reported to date, and those that have been reported usually have very small sample sizes. These conditions are worth bearing in mind when weighing the evidence.

Evidence of Harm

The arguments of those on all sides of the antioxidants during chemotherapy and/or radiation therapy issue revolve around the interaction of these agents with reactive oxygen species (ROS). Antioxidants reduce oxidative stress by functioning as free radical scavengers. Radiation therapy and some chemotherapeutic agents act by selective induction of oxidative stress through free radical production, which in turn mediates apoptosis.[1] Selective induction of apoptosis in cancer cells is a key goal of treatment. It could be argued that antioxidant supplements might interfere with this

VOLUME 8 • NUMBER 2 • FEBRUARY 2005 • PAGES 13-24

process by quenching the ROS that have been deliberately created.

A few studies dealing with specific aspects of this subject have been published. Witenberg and colleagues reported in 1999 that ascorbic acid (vitamin C) inhibited apoptosis in vitro in irradiated leukemia cells.[2] Salganik and colleagues showed in an animal model that depletion of antioxidants in the diet led to a predictable rise in observed reactive oxygen species.[3] From this they inferred that higher levels of antioxidants might interfere with cancer treatment by reducing levels of the necessary mediators of apoptosis. They further reasoned that high levels of antioxidants could be cancer-promoting in people exposed chronically to high levels of environmental carcinogens, by inhibiting normal apoptotic clearance of precancerous or cancerous cells. Wells and colleagues found in an in vitro model that treatment with ascorbic acid increased resistance to specific anticancer drugs in cell lines already known to be resistant.[4] There is a dearth of clinical studies to corroborate these laboratory findings.

Equivocal Evidence

A variation on the antioxidant-ROS model holds that while antioxidants may not have a positive or negative impact on the effect of cancer therapies, they might help to prevent incidental damage to healthy tissue. Blasiak and colleagues reported on an in vitro model in which vitamins C and E were used as a means of protecting normal cells during idarubicin therapy.[5] At fairly low concentrations (10 µM for vitamin C and 50 µM for vitamin E), lymphocytes treated with vitamin C showed significantly less DNA damage, but those treated with vitamin E did not.

Blanke and colleagues reported a case series in which nine patients with advanced malignancies were treated prophylactically with high doses of vitamin E (3,200 IU/d or about 2,100 mg/d) for 14 days prior to and during chemotherapy.[6] There was no measurable reduction in chemotherapy toxicity. Indeed, the authors noted that the most their findings could support was the conclusion that a maximal dose of vitamin E, when combined with chemotherapy, did not lead to a meaningful increase in symptoms of toxicity.

Wagdi et al randomized 25 patients, 13 receiving chemotherapy and 12 receiving radiation therapy, and with a variety of cancer types, to 1 g vitamin C and 600 mg vitamin E, or placebo.[7] The principal outcome of interest was cardiotoxicity. Neither group showed a significant drop in left ventricular ejection fraction (EF) (defined as > 10%). Although overall EF declined in the placebo arm and rose slightly in the active arm, the difference was not statistically significant. This replicated an earlier finding by Legha et al, in which a similar dose of vitamin E was used during adriamycin therapy.[8]

Weijl et al conducted a randomized study of the effects of vitamins C and E and selenium during cisplatin therapy.[9] Forty-eight patients with various kinds of cancer (not specified as to stage) received nutritional drinks twice a day beginning one week before the first chemotherapy dose. In the active arm, the drinks contained 1,000 mg vitamin C, 400 mg vitamin E, and 100 µg selenium. The main outcomes were reductions in nephro- and ototoxicity. No significant difference was noted in either dimension. They speculated that the lack of effect might have been dose-related.

Evidence of Benefit

The bulk of recent published opinion in favor of antioxidant use relies on a lack of clear evidence that antioxidant supplementation during chemo- and radiotherapy interferes with ROS-related therapeutic processes.[10] A few studies have even been interpreted to suggest that some antioxidants may enhance cancer cells' susceptibility to chemotherapeutic agents and/or radiation. Proponents of the use of antioxidants during chemotherapy suggest that antioxidants have a benefit

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/PUBLISHER: Brenda L. Mooney.
EDITORIAL GROUP HEAD: Lee Landenberger.
MANAGING EDITOR: Paula L. Cousins.
GST Registration Number: R128870672.

Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to *Alternative Medicine Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back Issues: $48 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

THOMSON
AMERICAN HEALTH CONSULTANTS

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@thomson.com
World-Wide Web: www.ahcpub.com

Subscription Prices

United States
$349 per year (Student/Resident rate: $165).
Multiple Copies
Discounts are available for multiple subscriptions. For pricing information, call Steve Vance at (404) 262-5511.
Outside the United States
$369 per year plus GST (Student/Resident rate: $180 plus GST).

Accreditation

Thomson American Health Consultants (AHC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Thomson American Health Consultants designates this educational activity for a maximum of 24 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the activity.

This CME activity was planned and produced in accordance with the ACCME Essentials. This CME activity is intended for physicians and researchers interested in complementary and alternative medicine. It is in effect for 36 months from the date of the publication.

Thomson American Health Consultants accepts pharmaceutical sponsorship of some programs but only in the form of unrestricted educational grants that meet all ACCME requirements.

For CME credit, add $50.

Questions & Comments

Please call **Paula Cousins,** Managing Editor, at (816) 960-3730 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Education guidelines, physicians have reported the following relationships with companies related to the field of study covered by this CME program. Dr. Gaudet, Dr. Heber, Dr. Jacobs, Dr. Keegan, Dr. Kemper, Dr. Kiefer, Dr. Kreitzer, Dr. Liebowitz, Dr. Sasser, and Dr. Schneider report no relationships with companies related to the field of study covered by this CME program. Dr. Greenfield is a consultant for Nature's Way, Inc., and serves on the scientific advisory board for Polaris, Inc. Dr. Vohra receives research funding from CIHR.
This publication does not receive commercial support.

over and above that of mitigating oxidative damage to normal tissue. They also argue that the benefit of such agents is only apparent with chronic treatment, beginning some time before chemotherapy. However, there remains considerable debate over which agents to use, in what doses, and during which stage of treatment.

Blumenthal et al administered a cocktail of vitamin A (3.5 IU/d), vitamin C (4 mg/d), and vitamin E (0.107 IU/d) to mice who were subsequently exposed to a single dose of radiation of varying sizes.[11] Treatment began 14 days before irradiation, and outcomes were assessed at seven and 14 days after exposure. Mice who received vitamin supplementation had a higher maximum sublethal dose of radiation and showed less loss of body weight. White blood cell counts were higher in the supplemented mice as early as day 7 post-exposure. A complicating factor with this study was the concomitant use of bone marrow transplantation in some of the mice. Another animal study, by Olas et al, used a pig blood model to test the protective effect of vitamin C on cells exposed to cisplatin.[12] They found that at a fairly high dose of vitamin C (3 mM), there was a significant reduction in oxidative damage to platelets.

There is some evidence of benefit from observational studies. Branda et al collected questionnaire data from 49 women with breast cancer, irrespective of stage.[13] Although the focus of the study was vitamin B_{12} and folate, information about other micronutrients also was recorded. Forty-seven percent of respondents reported taking a multivitamin, 22% reported taking vitamin C, and 37% reported taking vitamin E. Both those reporting multivitamin or vitamin E supplementation, and those in a historical control group showed a drop in neutrophils during chemotherapy, but the drop in those reporting supplement use was attenuated to a statistically significant degree. This result is interesting, but somewhat limited by the way the data were collected and by the use of non-contemporaneous controls.

Another observational study followed 103 children in treatment for acute lymphoblastic leukemia for a period of six months.[14] Assessment of antioxidant intake was made by 24-hour food recall and food frequency questionnaires, and by serum analysis at three-month intervals. Substances reported included vitamins A, C, and E, as well as beta-carotene and types of cholesterol known to mediate inflammation. Vitamin A intake declined significantly ($P = 0.04$) over the study period from 724 ± 29 µg to 645 ± 31 µg. Average vitamin C intake declined from 92 ± 5 mg/d to 83 ± 6 mg/d, though the change was not significant. Vitamin E intake also declined from an average of 6.7 ± 0.2 mg to 6.3 ± 0.2 mg. Interestingly, plasma concentrations increased (vitamin A and total carotenoids) or were static (all others) over the course of the study.

At various measured intervals, intake of all agents was associated with a statistically significant reduction in chemotherapy-related side effects. However, when intake was averaged over the whole study period, only the association with beta-carotene remained significant. Very few of the studied patients (< 4%) took supplements at any time, so the majority of antioxidant intake was in the form of food. The nausea and other digestive disturbances associated with chemotherapy would suggest that these findings are better described as correlative than causative.

A number of small clinical studies also have lent support to the "protective" camp. Ludwig et al reported that in a series of eight patients, a cream containing DMSO and vitamin E appeared to minimize skin ulceration secondary to extravasation of chemotherapy agents known to cause such irritation.[15]

Wadleigh and colleagues used a topical vitamin E preparation to treat oral mucositis in patients receiving chemotherapy.[16] Sixty-seven percent of patients (6/9) on active therapy showed complete resolution of oral lesions, as compared to 11% (1/9) of those using placebo cream. Although the difference was statistically significant, the small sample size combined with the heterogeneity of cancer types makes the result difficult to generalize.

Pace et al randomly assigned 47 patients with solid tumors to cisplatin therapy, or cisplatin plus vitamin E (300 mg/d).[17] Vitamin E supplementation began between one and eight days (mean = 4) before the start of cisplatin therapy. The cumulative incidence of neurotoxicity, measured by the neurological symptom score, was the main outcome. Incidence in the vitamin E group was significantly lower than in the control group (30.7% vs. 85.7%, $P < 0.01$).

One published report lends support to the notion of an anticancer role for antioxidants independent of other agents. An in vitro study by Piyathilake and colleagues used human tissue collected from 22 individuals with primary cancers of the lung and larynx.[18] They reported the intriguing finding that cancer cells appear to accumulate vitamin C at higher rates than normal cells. Further, there was a statistically significant inverse association between vitamin C concentrations and DNA methylation, a marker of malignant change.

Limitations of the Available Evidence

None of the reports published to date meets all of the requirements of convincing scientific evidence—an adequately powered study, conducted in a homogeneous

group of human subjects, testing a single intervention while holding everything else as constant as possible. It is perhaps unreasonable to expect this, given the nature of cancer treatment. Few if any kinds of cancer are invariably treated with a single compound or the same combination of compounds, in the same doses, on the same schedule. The challenge of finding a large enough group of patients with the same kind of cancer, at the same stage, in a reasonable time, is daunting for most single-center studies. The lack of a well-funded and research-oriented industry (as exists for pharmaceuticals and medical devices) to back vitamin research is a limiting factor to the setting up and running of large-scale multicenter trials. Yet these practical factors leave the literature in this area without a clear consensus.

Conclusion

It would appear that *in medio stat virtus* is the best guiding principle for clinical advice. There does not seem to be strong evidence that antioxidant supplements in moderate quantities interfere with the action of chemo- or radiotherapy. If anything, the evidence suggests that cancer treatment depletes the body's normal levels of these agents. Super-dietary supplementation may be indicated just to maintain daily recommended intake levels. At the same time, the evidence that antioxidants have a positive interactive relationship with cancer therapies, or that they have independent anticancer properties, is still more suggestive than demonstrative. Very large doses of antioxidants (and other micronutrients) have toxicities that may make them dangerous for anyone, not just cancer patients.

Recommendation

Vitamin supplements are readily available over the counter. Both patients with newly found and long-standing interest in their health may seek out such products as part of a response to the diagnosis of cancer. It is important for the clinician to establish and maintain communication with his/her patients about what they are taking. Because supplements vary widely in potency, purity, and formulation, it is also important for the clinician to be familiar enough with brands and their reputations to give sound advice when asked.

Ultimately, the primary care physician's recommendations must be guided by patient preference and by deference to the opinion of the treating oncologist. It is not fair to involve the patient in a tug-of-war between physicians with differing philosophies. Although conventional chemotherapeutic agents are far from perfect, there is as yet no micronutrient with a comparably large body of experimental evidence. Until there is, when a choice must be made, the conventional therapies should take precedence. ❖

Dr. Sasser is Director, Research Epidemiology, R. Stuart Dickson Institute for Health Studies, Carolinas HealthCare System, Charlotte, NC.

References

1. Labriola D, Livingston R. Possible interactions between dietary antioxidants and chemotherapy. *Oncology* 1999; 13:1003-1008.
2. Witenberg B, et al. Ascorbic acid inhibits apoptosis induced by X irradiation in HL60 myeloid leukemia cells. *Radiat Res* 1999;152:468-478.
3. Salganik RI. The benefits and hazards of antioxidants: Controlling apoptosis and other protective mechanisms in cancer patients and the human population. *J Am Coll Nutr* 2001; 20:464S-472S; discussion 473S-475S.
4. Wells WW, et al. Ascorbic acid and cell survival of adriamycin resistant and sensitive MCF-7 breast tumor cells. *Free Radic Biol Med* 1995;18:699-708.
5. Blasiak J, et al. Genotoxicity of idarubicin and its modulation by vitamins C and E and amifostine. *Chem Biol Interact* 2002;140:1-18.
6. Blanke CD, et al. A phase I study of vitamin E, 5-fluouro-uracil and leucovorin for advanced malignancies. *Invest New Drugs* 2001;19:21-27.
7. Wagdi P, et al. Cardioprotection in patients undergoing hemo- and/or radiotherapy for neoplastic disease. A pilot study. *Jpn Heart J* 1996;37:353-359.
8. Legha SS, et al. Clinical and pharmacologic investigation of the effects of alpha-tocopherol on adriamycin cardiotoxicity. *Ann N Y Acad Sci* 1982;393:411-418.
9. Weijl NI, et al. Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: A randomised, double-blind, placebo-controlled study. *Eur J Cancer* 2004; 40:1713-1723.
10. McCall MR, Frei B. Can antioxidant vitamins materially reduce oxidative damage in humans? *Free Radic Biol Med* 1999;26:1034-1053.
11. Blumenthal RD, et al. Anti-oxidant vitamins reduce normal tissue toxicity induced by radio-immunotherapy. *Int J Cancer* 2000;86:276-280.
12. Olas B, et al. Vitamin C suppresses the cisplatin toxicity on blood platelets. *Anticancer Drugs* 2000;11:487-493.
13. Branda RF, et al. Effect of vitamin B_{12}, folate, and dietary supplements on breast carcinoma chemotherapy—induced mucositis and neutropenia. *Cancer* 2004;101:1058-1064.
14. Kennedy DD, et al. 2004. Low antioxidant vitamin intakes are associated with increases in adverse effects of chemotherapy in children with acute lymphoblastic leukemia. *Am J Clin Nutr* 2004;79:1029-1036.
15. Ludwig CU, et al. Prevention of cytotoxic drug induced skin ulcers with dimethyl sulfoxide (DMSO) and alpha-tocopherole. *Eur J Cancer Clin Oncol* 1987;23:327-329.

16. Wadleigh RG, et al. Vitamin E in the treatment of chemotherapy-induced mucositis. *Am J Med* 1992;92:481-484.
17. Pace A, et al. 2003. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin therapy. *J Clin Oncol* 2003;21:927-931.
18. Piyathilake CJ, et al. The accumulation of ascorbic acid by squamous cell carcinomas of the lung and larynx is associated with global methylation of DNA. *Cancer* 2000;89:171-176.

Complementary and Alternative Therapies and End-of-Life Care

PART I OF A SERIES ON END-OF-LIFE CARE

By Lynn Keegan, RN, PhD, HNC, FAAN

THE RAPID PACE OF ADVANCES IN MEDICAL TECHNOLOGY during the past few decades has brought with it a host of ethical dilemmas regarding when and how to use new therapies, especially with regard to end-of-life (EOL) care. Procedures and medications developed for resuscitative events, chemotherapy directed toward cancer treatment, antibiotics aimed at acute infectious disease, radiologic treatment for conquerable tumors, and an arsenal of other modern medical marvels are used not only on the salvageable patient, but also on those who are terminal.

The irony is that simultaneous with the development and use of these technological advances, patients have turned to complementary and alternative medicine (CAM) therapies in ever-increasing numbers. While the utility of many CAM therapies is still very much in question and being investigated by researchers, some CAM treatments, by virtue of the comfort they provide, may have a place in the holistic care of patients in the final stages of life.

Aggressive Conventional Cancer Treatment Near End of Life

A recent study of 28,777 cancer patients across four years found the proportion still receiving chemotherapy within two weeks of death increased from 13.8% to 18.5% over the course of the study, and the percentage that started a new chemotherapy regimen in the last 30 days of life increased from 4.9% to 5.7%.[1] Concurrent with this increased use of chemotherapy during the final stages of life were increasing numbers of patients with more than one emergency room visit, admissions to the hospital, and admissions to intensive care units in the last month of life. Moreover, those who were treated with chemotherapy were admitted to hospice when they were closer to death and were more likely to die in a hospital (34.9% vs. 29.0%, $P < 0.001$) than those not receiving chemotherapy.

Just by living in an area with more teaching hospitals per capita independently predicted more aggressive care in patients either on or off chemotherapy. On the other hand, a higher density of hospices in an area was associated with a significant, independent decrease in the likelihood of experiencing an indicator of aggressive care.[1]

Findings from focus groups of bereaved relatives, who have the perspective of having seen the full course of disease, reflected a sense that continuation of cancer treatment until very late in the disease prevented them and their loved one from realistically coming to terms with the inexorable progression of the disease.[2] This study supports the argument that in some cases aggressive medical treatment continues too long, delaying or depriving patients of the opportunity for transition from active medical treatment to supportive EOL care.

End-of-Life Suffering

Most deaths in the United States occur in the context of chronic diseases in later life and often are accompanied by potentially remediable emotional or physical suffering.[3] Suffering is traditionally viewed as a state encompassing psychological distress, spiritual concerns, and various aspects of physical pain.

An Israeli study was initiated to evaluate the suffering of terminal dementia patients over the time period from admission to the last day of life.[4] The study included consecutive end-stage dementia patients dying in a general geriatric department of a tertiary hospital. Patients were evaluated weekly by the Mini Suffering State Examination scale (MSSE). Seventy-one patients were studied. Mean survival of patients was 38.0 ± 5.1 days. MSSE increased during hospital stays from 5.62 ± 2.31 to 6.89 ± 1.95 ($P < 0.001$). According to the MSSE scale, 63.4% and 29.6% of patients died with high and intermediate levels of suffering, respectively. Only 7% of the patients died with a low level of suffering. The researchers concluded that despite traditional medical and nursing care, a large proportion of people dying with dementia experienced an increasing amount of suffering as they approached death.[5]

Analysis in one study revealed six themes important to people with advanced cancer diagnoses:[6]

- protection of dignity,
- control of pain and other symptoms associated with disease,

- management of treatment,
- management of how remaining time is spent,
- management of impact on family, and
- control over the dying process.

The Goal for End of Life Care

Achieving a peaceful and comfortable death for patients must be a priority.[5] Specific imagery scripts, ritual exercises, massage therapy, and guided imagery are examples of CAM therapies available to support this mission. A patient with terminal illness and pain could receive not only medication for pain control, but also hypnosis, music therapy, acupuncture/acupressure, or massage. Toward the end of life, palliative care should generally increase in line with increasing symptoms and other problems.

Fortunately, there is increasing recognition of the importance of high-quality symptomatic care and support near EOL.[7] For example, the state of California now requires 12 continuing medical education credits in pain management and EOL care for nearly all physicians.

Efficacy of CAM at End of Life

A comprehensive investigation studying the efficacy of CAM modalities in treating pain, dyspnea, and nausea and vomiting in patients near the EOL evaluated 21 independent analyses of symptomatic adult patients with incurable conditions. Original articles were evaluated following a search through MEDLINE, CancerLIT, AIDSLINE, PsycLIT, CINAHL, and Social Work Abstracts databases.[8] Eleven were randomized controlled trials, two were non-randomized controlled trials, and eight were case series. The investigators concluded that acupuncture, transcutaneous electrical nerve stimulation, supportive group therapy, self-hypnosis, and massage therapy may provide pain relief for those with cancer and people in the process of dying. Data also suggest that relaxation/imagery can improve oral mucositis pain, and that patients with severe chronic obstructive pulmonary disease may benefit from the use of acupuncture, acupressure, and muscle relaxation with breathing retraining to relieve dyspnea.

Pain Management and End-of-Life Care

Pain at the EOL is usually treatable, but many dying patients are under-treated and die in unnecessary pain. The most important factor in EOL care is for practitioners to make pain control a matter of paramount importance.[9] Institutional standards for pain management often address only the physical aspects of pain. Effective pain management requires assessment and interventions that address the multidimensional nature of pain, suffering, and quality of life.[10,11]

What is still lacking are evidence-based data indicating which CAM therapies work best and why. To date, most articles on CAM for EOL issues are surveys, opinions, or anecdotal accounts. There is a critical need for more investigation in this area.

Hypnosis or Hypnotherapy

Hypnosis or hypnotherapy is one area where there have been some investigations.

One study evaluated the use of hypnotically facilitated medical therapy in the management of intractable pain, nausea, and vomiting in three terminally ill cancer patients.[12] The existential principles of death anxiety, isolation, and meaninglessness were addressed with a combination of classic and Ericksonian hypnotherapy techniques. The intractable nature of the presenting physical symptoms was seen as a possible manifestation of the impact of the terminal prognosis. Direct hypnotic suggestions for the management of pain, nausea, and vomiting were avoided. It was hypothesized that, as the existential conflicts associated with the patients' terminal status resolved, the physiological symptoms would become responsive to medication. After six sessions grounded in the principles of existential psychotherapy, the intractable status of the physical symptomatology remitted, and the patients responded to medical management. Hence, in this small pilot study, hypnotherapy was useful for mediating somatic and psychosomatic symptomatology.

Symptoms relating to psychological distress are even more prevalent than pain and other physical symptoms among those with life-limiting conditions. At one clinical teaching center, a four-stage model helps clinicians develop and implement appropriate hypnotherapeutic treatment for patients with incurable disease.[13] The primary focus of the hypnotherapy is to ameliorate pain and dyspnea to restore a level of psychological and physical well-being. Other focuses include assisting patients with psychological adjustment to their incurable and ultimately final state.

One New York hospital uses hypnosis with terminal patients to attain relaxation, overcome insomnia, and achieve pain relief.[14] Of particular importance, hypnosis is used to teach the patient to work with relatives, and others close to them, as caregivers in a special relationship and a very important source of relief to the patient.

Music Therapy

Music is another CAM therapy that has some documented EOL benefits, but methodologically sound studies are few and far between.

The expression and discussion of feelings of loss and grief can be very difficult for terminally ill patients, yet it is believed that by expressing emotions patients experience a more relaxed and comfortable state. Case examples of three in-patient palliative care clients at a Canadian geriatric care center have been cited.[15] Techniques were used to assist clients to express their thoughts and feelings using music therapy. The goals set for these patients were to decrease depressive symptoms and social isolation, increase communication and self-expression, stimulate reminiscence and life review, and enhance relaxation. All three subjects were successful in reaching their individual goals.

An Australian research team investigated the utility of music therapy in a cancer hospital over a three-month period.[16] Criterion sampling was used to elicit interpretations from five sources: 128 patients who participated, 27 patients who overheard or witnessed music therapy, 41 visitors, 61 staff, and the music therapist-researcher. Fifty-seven percent of the patients who participated had advanced or end-stage cancer. The music therapist's interpretations were recorded in a clinical journal and the respondents' interpretations were written on anonymous open-ended questionnaires. Thematic and content analyses were performed on the five groups of data with the support of qualitative data management software. Findings from the five data groups were contrasted and compared. Respondents reported that affective, contemplative, and imagined moments during music therapy affirmed their "aliveness," resonating with an expanded consciousness.

A more rigorous U.S. study was done to evaluate the effects of music therapy on quality of life, length of life in care, physical status, and relationship of death occurrence to the final music therapy interventions of hospice patients diagnosed with terminal cancer.[17] Subjects were adults with terminal cancer who were living in their homes and receiving hospice care. A total of 80 subjects participated in the study and were randomly assigned to one of two groups: experimental (routine hospice services and clinical music therapy) and control (routine hospice services only). Groups were matched on the basis of gender and age. Quality of life was measured by the Hospice Quality of Life Index-Revised (HQOLI-R), a self-report measure given at every visit. Functional status of the subjects was assessed by the hospice nurse during every visit using the Palliative Performance Scale. All subjects received at least two visits and quality-of-life and physical status assessments. Repeated-measures ANOVA revealed a significant difference between groups on self-reported quality-of-life scores for visits one and two. Quality of life was higher for those subjects receiving music therapy, and their quality of life increased over time as they received more music therapy sessions. Subjects in the control group, however, experienced a lower quality of life than those in the experimental group, and their quality of life decreased over time. There were no significant differences in results by age or gender of subjects. Also, there were no significant differences between groups on physical functioning, length of life, or time of death in relation to the last scheduled visit by the music therapist or counselor.

A Chinese study observed the clinical effects of music therapy while treating patients with cancer.[18] Music therapy combined with antitumor drugs, including chemotherapy and Chinese drugs, was given to 162 cancer patients to observe the change in self-rating depression scale (SDS), self-rating anxiety scale (SAS), Minnesota Multiphasic Personality Inventory (MMPI), Hamilton Rating Scale for Depression (HAMD), and T lymphocyte subsets and NK cell antitumor activity. Forty-six patients not receiving music therapy were used as the control group. Results of the scale marks of SDS and SAS in the experimental group after treatment were significantly lower than that of the control group ($P < 0.05$, $P < 0.01$). After treatment, the average values of MMPI on falseness, hypochondriasis, and depression in the treated group were all improved ($P < 0.01$ or $P < 0.05$), but in the control group significant difference only showed for hypochondriasis ($P < 0.05$). HAMD in the treated group revealed some improvement in insomnia, early awakening, daily work and interest, systemic symptoms, and hypochondriasis ($P < 0.05$), and significant improvement in depression, difficulty in falling asleep, psychiatric anxiety, and somatic anxiety ($P < 0.01$). In the control group, only work interest and hypochondriasis had some improvement ($P < 0.05$). Percent CD8 was reduced in both groups after treatment ($P < 0.01$), but in the treated group CD3, CD4, and CD4/CD8 ratio were not significantly changed after treatment ($P > 0.05$), while in the control group they decreased ($P < 0.05$). NK cell activity in the treated group before and after treatment was not significantly lowered ($P > 0.05$), while in the control group there was a significant lowering after treatment ($P < 0.05$). The researchers concluded that music therapy could regulate the emotions of cancer patients, optimize emotional affect, improve somatic symptoms, enhance immune function, and raise the self-regulating power in the body.

A 2003 U.S. nursing study tested the hypotheses that the effects of a music intervention are greater than those of simple distraction, and that either intervention is better at controlling procedural pain and anxiety than treatment as usual.[19] The randomized, controlled experiment

in a Midwestern comprehensive cancer center studied 58 people with cancer having noxious medical procedures, such as tissue biopsy or port placement. Participants completed measures of pain and anxiety before and after their medical procedures and provided a rating of perceived control over pain and anxiety after the procedure. Outcomes achieved with music did not differ from those achieved with simple distraction. Moreover, outcomes achieved under treatment as usual were not significantly different from those obtained with music or distraction interventions. Some patients found that the music interventions were bothersome and reported that they wanted to attend to the activities of the surgeon and the medical procedure itself. The researcher concluded that the effects of music, distraction, and treatment as usual are equivalent. In addition, individual patient preference must be honored. This study suggests that health care providers must be sensitive to the various likes and dislikes of patients regarding music styles, and that some people may not like or respond to music at all.

[Part 2 of this series, examining the roles of acupuncture and massage in end-of-life care, will appear in the March issue of Alternative Medicine Alert*.]* ❖

Dr. Keegan is Director, Holistic Nursing Consultants, Port Angeles, WA.

References

1. Earle CC, et al. Trends in the aggressiveness of cancer care near the end of life. *J Clin Oncol* 2004;22:315-321.
2. Earle CC, et al. Increasing aggressiveness of cancer treatment near the end of life: Is it a quality of care issue? *Am J Oncol Rev* 2004;3:401-403.
3. Lyness JM. End-of-life care: Issues relevant to the geriatric psychiatrist. *Am J Geriatr Psychiatry* 2004;12:457-472.
4. Aminoff BZ, Adunsky A. Dying dementia patients: Too much suffering, too little palliation. *Am J Alzheimers Dis Other Demen* 2004;19:243-247.
5. Kaya E, Feuer D. Prostate cancer: Palliative care and pain relief. *Prostate Cancer Prostatic Dis* 2004;7:311-315.
6. Volker DL, et al. Patient control and end-of-life care. Part II: The advanced practice nurse perspective. *Oncol Nurs Forum* 2004;31:954-960.
7. Institute of Medicine. *Improving Palliative Care for cancer*. Washington, DC: National Academy Press; 2001.
8. Pan CX, et al. Complementary and alternative medicine in the management of pain, dyspnea, and nausea and vomiting near the end of life. A systematic review. *J Pain Symptom Manage* 2000;20:374-387.
9. Anderson CM. Pain relief at the end-of-life: A clinical guide. *Mo Med* 2002;99:556-559.
10. Deng G, et al. Complementary therapies for cancer-related symptoms. *J Support Oncol* 2004;2:419-426; discussion 427-429.
11. Lynch M, Abrahm J. Ensuring a good death. *Cancer Pract* 2002;10(Suppl 1):S33-S38.
12. Iglesias A. Hypnosis and existential psychotherapy with end-stage terminally ill patients. *Am J Clin Hypn* 2004;46: 201-213.
13. Marcus J, et al. The integration of hypnosis into a model of palliative care. *Integr Cancer Ther* 2003;2:365-370.
14. Douglas DB. Hypnosis: Useful, neglected, available. *Am J Hosp Palliat Care* 1999;16:665-670.
15. Clements-Cortes A. The use of music in facilitating emotional expression in the terminally ill. *Am J Hosp Palliat Care* 2004;21:255-260.
16. O'Callaghan C, McDermott F. Music therapy's relevance in a cancer hospital researched through a constructivist lens. *J Music Ther* 2004;41:151-185.
17. Hilliard RE. The effects of music therapy on the quality and length of life of people diagnosed with terminal cancer. *J Music Ther* 2003;40:113-137.
18. Cai GR, et al. Clinical observation of music therapy combined with anti-tumor drugs in treating 116 cases of tumor patients. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2001;21: 891-894.
19. Kwekkeboom KL. Music versus distraction for procedural pain and anxiety in patients with cancer. *Oncol Nurs Forum* 2003;30:433-440.

Cat's Claw: Traditional and Clinical Uses

By David Kiefer, MD

CAT'S CLAW, AN HERBAL MEDICINE USUALLY FORMULated from two species of the genus *Uncaria* that are found primarily in Peru and Ecuador, has a rich ethnobotanical history and recent scientific investigations have examined its physiological and possible clinical effects. Marketing of cat's claw products abounds (an internet Google search yields 279,000 hits under the name cat's claw), though officially, consumers only spent $289,000 on cat's claw in 2003, 13.5% less than the year before.[1]

History and Traditional Use

Cat's claw, or as the Spanish call it "uña de gato," derives its name from the shape of curved thorns that protrude from the vine of plants in the genus *Uncaria*. One of the species, *Uncaria tomentosa*, is an important medicinal plant in the pharmacopoeia of the Asháninka Indians in Peru.[2] *U. tomentosa* also is referred to as "savéntaro," or powerful plant, and as such was believed to possess good spirits that could repair disruptions in body-spirit interactions with such conditions as anxiety.[2]

Indeed, specialized healers in Peru boiled sliced root bark of *U. tomentosa* to create a bitter medicinal drink to address anxiety. It also was used for a variety of other health problems, including abscesses, asthma, cancer, fevers, urinary tract infections, rheumatism, gastric ulcers, weakness, and contraception.[2,3]

Most sources list another species, *U. guianensis*, as having the same traditional uses with minor differences such as the leaves being used to enhance the healing of wounds, and an extract used for dysentery.[4]

There are many stories about the discovery of cat's claw in South America by foreign priests and ethnobotanists who described miraculous cures that then prompted the marketing and export of cat's claw products to Europe and North America.

Botany and Pharmacology

There are 34 species in the genus *Uncaria* (Family Rubiaceae, a family that also includes coffee, ipecac, and quinine), 29 in southeast Asia, one in Africa, and the two from Central and South America that are relevant to cat's claw products available today (*U. tomentosa* and *U. guianensis*). These plants generally are large woody vines (called lianas) typically found in second-growth forest types,[5] and can reach several inches in diameter and 1,000 feet in height.[6]

U. tomentosa and *U. guianensis* contain a variety of compounds, including 17 different alkaloids, terpenoids (including quinovic acid glycosides), tannins, flavonoids, and sterols.[6] The primary alkaloids are oxindole and indole alkaloids, both of which exist either as a pentacyclic or tetracyclic form. The composition of these compounds varies between plants, plant parts (i.e., roots vs. leaves), young vs. mature leaves, and when the plant is harvested in different seasons.[3,4,7] Also, isomerization takes place among the pentacyclic oxindole alkaloids, some of which are more stable than others, or last longer after harvesting,[3] which makes the evaluation of the activity of the individual compounds (isomers) difficult.[7]

There may be two specific genotypes of *U. tomentosa*; one chemotype with pentacyclic oxindole alkaloids and the other with tetracyclic oxindole alkaloids.[2] Many of the beneficial physiological effects are due to the pentacyclic oxindole alkaloids, while the tetracyclic oxindole alkaloids may act as competitive antagonists.[4,7] Therefore, it is important to correctly identify the chemotype during the manufacturing process. Interestingly, though the two plant chemotypes are botanically identical, when cat's claw is prepared by Asháninka healer-priests, they exclusively choose the pentacyclic oxindole alkaloid type by a process that is still unknown to modern researchers.[2,7]

Most products marketed in the United States are based on *U. tomentosa* due to its higher alkaloid content and, therefore, easier standardization.[8]

Mechanism of Action

Researchers believe that the physiological effects of *U. tomentosa* and *U. guianensis* are due to the oxindole alkaloids, especially those of the pentacyclic type.[6]

Oxindole alkaloids may not account for all of the physiological effects of cat's claw. One set of in vitro and in vivo (rat) experiments on freeze-dried aqueous extracts of cat's claw showed that *U. guianensis* has more potent antioxidant and anti-inflammatory effects than *U. tomentosa*, despite having fewer oxindole alkaloids.[8] Others point out that the use of cat's claw to treat chronic inflammation doesn't fit with the fact that some of the oxindole alkaloids promote phagocytosis.

Other research focuses on the antioxidant and anticancer activities of cat's claw. Aqueous and freeze-dried extracts of *U. tomentosa* may act to suppress TNF-alpha and NK-kappa-B,[9] and C-Med-100®, an ultrafiltered water extract of inner and outer bark from *U. tomentosa* (standardized to with 8-10% carboxy alkyl esters, less than 0.05% oxindole alkaloids), may lead to prolonged lymphocyte survival.[10] One in vitro study found that methanolic extracts of *U. tomentosa* had a higher antiproliferative effect on one breast cancer cell line than aqueous extracts.[11]

A series of the terpenoid compounds, quinovic acids, may have some interesting antiviral effects, such as against rhinoviruses or vesicular stomatitis virus as shown in in vitro studies, as well as anti-inflammatory effects.[2]

Clinical Studies

Only a few small clinical studies have been conducted on the use of cat's claw. In one study, with a goal of testing the immunomodulatory effects of cat's claw, researchers conducted a double-blind, randomized controlled trial on 40 patients with rheumatoid arthritis.[12] Patients either received one 20 mg capsule three times daily of *U. tomentosa* root extract (14.7 mg/g pentacyclic oxindole alkaloids, and no tetracyclic oxindole alkaloids, marketed as Krallendorn® capsules) or placebo for six months. Patients were permitted to stay on their regular medication; equal numbers of patients in each group were on sulfasalazine or hydroxychloroquine, and prednisolone. The results showed that the patients in the treatment group experienced fewer painful joints than the control group, with no significant difference in the number of swollen joints or the duration of morning stiffness. The group treated

with *U. tomentosa* did not demonstrate a change in the laboratory values tested. Despite the small size of this trial, the results indicated that *U. tomentosa* may have a role as an adjuvant in the treatment of rheumatoid arthritis.

Another study examined the use of a freeze-dried preparation of *U. guianensis* bark for osteoarthritis of the knee.[13] Forty-five people were randomized to receive either 100 mg daily of the cat's claw preparation (n = 30) or placebo (n = 15) over four weeks in a double-blind prospective trial, assessing effects on pain at rest, at night, and during exercise. The cat's claw group had significantly less knee pain with activity, even after just one week of treatment. Furthermore, a combined extract of *U. guianensis* and *U. tomentosa* was tested using a variety of physiological assays and demonstrated antioxidant activity via free radical scavenging effects, inhibition of TNF production, and possibly cyclooxygenase-2 inhibition.

Another trial compared the response to pneumococcal vaccine in 23 Caucasian male volunteers 40-60 years old who were randomized to receive either 350 mg twice daily of a standardized extract of *U. tomentosa* (C-Med-100) for two months, or placebo.[14] Blood tests and a physical exam were done on study participants day 0, 30, and 60; a pneumococcal vaccine (23 valent Pneumovax) was administered on day 30. Titers were drawn again at day 180. Baseline characteristics were not identical; the control group had a greater percentage of natural pneumococcal antibodies, biasing the response expected from the two groups in the initial phase of the study. Despite this, the treatment group showed no loss in immune response at the five month blood test check as compared to the control group, and there was a slight increase in percentage of lymphocytes compared to neutrophils in blood tests of the cat's claw-treated group.

Dosages and Forms

The specific therapeutic dose of cat's claw remains unclear. The traditional preparation involves slowly boiling the bark of the roots or stems to prepare a drinkable decoction.[3] Tinctures are dosed 1 mL one to three times daily, and 500-2,000 mg of dry extracts are mixed in water one to three times daily.[6] There are also standardized extracts, some of which have been used in preclinical and clinical research as mentioned above. For example, the root extract used in the rheumatoid arthritis study (Krallendorn) is free of tetracyclic oxindole alkaloids and is dosed at 20 mg three times daily. The patented extract C-Med-100 is dosed at 300 mg daily. There is also a low-molecular-weight fraction, hot-water extract from the whole plant (8% carboxyl alkyl esters) dosed at 100 mg three times daily.[6]

Adverse Effects, Contraindications, and Drug Interactions

The side effects reported for cat's claw in the clinical research trials are mild; slight gastrointestinal upset, dizziness, and headache have been reported, but were not significantly different from that noted for placebo groups. If cat's claw is ingested as a tea or crude extract, its bitterness may cause mild nausea.[6]

Until more information is available, most authorities recommend against using cat's claw in autoimmune diseases due to its immunomodulating activities.[6,15] Similarly, cat's claw should be avoided in patients with pending organ transplantation or skin grafts, or during immunosuppressive therapy. Caution should be exercised in patients taking antihypertensives due to the fact that some of the phytochemicals in cat's claw have known hypotensive activity.[6,13] Due to the traditional use as a contraceptive, and because one of the alkaloids acts as a uterine stimulant (rhynchophylline), cat's claw should be avoided during pregnancy.[16] Also, until more information about the physiological effects of cat's claw is known, such as its effects on immature immune systems, its use should be avoided during lactation and for children younger than age 3.[6,7,14]

There is one case report of cat's claw use being chronologically associated with acute renal failure in a woman with systemic lupus erythematosus.[17] However, there was no discussion of the correct species, the form used, the dose, or any relevant admixtures of the botanical preparation used, making it difficult to interpret what actually happened in this person's case.

Conclusion

Cat's claw is an interesting botanical medicine based on two species found in Latin America, *Uncaria tomentosa* and *Uncaria guianensis*. In vitro and in vivo animal research show that the pentacyclic oxindole alkaloids appear particularly important as immune system stimulants, and whole plant extracts act as strong antioxidants and anti-inflammatories, perhaps through their effects on TNF-alpha. Although extracts of the root and stem bark were used traditionally, some results indicate that the leaf extracts also may be effective, and *U. guianensis* may be the more potent plant, despite having lower levels of oxindole alkaloids.

There are a few small clinical trials of interest suggesting that cat's claw may be useful as an adjuvant treatment for both rheumatoid arthritis (*U. tomentosa*) and for osteoarthritic knee pain (*U. guianensis*), and as a

boost to the immune response after pneumococcal vaccination (*U. tomentosa*). Various forms of the this plant are utilized, the most effective of which is still being determined. However, it does appear that an extract free of tetracyclic oxindole alkaloids (which antagonize the effects of pentacyclic compounds) is preferable.

Several cautions for the use of cat's claw, including treatment of hypertension, or in autoimmune disease, pregnancy, lactation, and for children younger than age 3, are based primarily on the physiological actions of its constituents or extracts, though only mild side effects have been reported in humans.

Recommendation

Cat's claw (*Uncaria tomentosa* or *Uncaria guianensis*) is an herbal medicine with an interesting history of traditional use in Latin America, some recent physiological research that points to possible antioxidant, anticancer, anti-inflammatory, and immune system effects, and a few small positive clinical trials. However, there remain many aspects of this plant that need clarification, such as formulations and dose most effective for clinical use, the exact physiological effects, and its safety profile. At present there are insufficient data to provide specific recommendations regarding appropriate therapeutic use. Practitioners would do well to wait for additional research before employing cat's claw except in unique clinical circumstances. ❖

Dr. Kiefer recently completed a fellowship at the Program in Integrative Medicine, College of Medicine, University of Arizona, Tucson.

References

1. Total Herbal Supplement Categories & Subcategories. *The Natural Foods Merchandiser* June 2004.
2. Keplinger K, et al. *Uncaria tomentosa* (Willd.) DC.—ethnomedicinal use and new pharmacological, toxicological and botanical results. *J Ethnopharmacol* 1999;64:23-34.
3. Laus G, et al. Alkaloids of Peruvian *Uncaria tomentosa*. *Phytochemistry* 1997;45:855-860.
4. Laus G. Advances in chemistry and bioactivity of the genus *Uncaria*. *Phytother Res* 2004;18:259-274.
5. Gentry AH. *A Field Guide to the Families and Genera of Woody Plants of Northwest South America.* Washington, DC: Conservation International; 1993.
6. Williams JE. Review of antiviral and immunomodulating properties of plants of the Peruvian rainforest with a particular emphasis on Una de Gato and Sangre de Grado. *Altern Med Rev* 2001;6:567-579.
7. Reinhard KH. *Uncaria tomentosa* (Willd.) D.C.: Cat's claw, uña de gato, or savéntaro. *J Altern Complement Med* 1999; 5:143-151.
8. Sandoval M, et al. Anti-inflammatory and antioxidant activities of cat's claw (*Uncaria tomentosa* and *Uncaria guianensis*) are independent of their alkaloid content. *Phytomedicine* 2002;9:325-337.
9. Sandoval M, et al. Cat's claw inhibits TNFalpha production and scavenges free radicals: Role in cytoprotection. *Free Radic Biol Med* 2000;29:71-78.
10. Akesson C, et al. C-Med 100, a hot water extract of *Uncaria tomentosa*, prolongs lymphocyte survival in vivo. *Phytomedicine* 2003;10:23-33.
11. Riva L, et al. The antiproliferative effects of *Uncaria tomentosa* extracts and fractions on the growth of breast cancer cell line. *Anticancer Res* 2001;21(4A):2457-2461.
12. Mur E, et al. Randomized double blind trial of an extract from the pentacyclic alkaloid-chemotype of *Uncaria*

CME Questions

CME Instructions: Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a certificate of completion. When an evaluation form is received, a certificate will be mailed to the participant.

4. Which of the following statements about antioxidant intake during chemo- or radiotherapy is *true*?

a. There does not seem to be strong evidence that antioxidant supplementation in moderate quantities interferes with chemo- or radiotherapy.
b. Cancer treatment depletes the body's normal antioxidant levels.
c. Super-supplementation may be indicated to maintain daily intake levels of antioxidants during chemo- and radiotherapy.
d. All of the above

5. Toward the end of life, palliative care generally should increase in line with increasing symptoms and other problems.

a. True
b. False

6. A few small studies suggest that cat's claw may be useful:

a. as an adjuvant treatment for rheumatoid arthritis.
b. as an adjuvant treatment for osteoarthritic knee pain.
c. to boost the immune response after pneumococcal vaccination.
d. All of the above

Answers: 4. d, 5. a, 6. d.

13. Mur E, et al. Randomized double blind trial of an extract from the pentacyclic alkaloid-chemotype of *Uncaria tomentosa* for the treatment of rheumatoid arthritis. *J Rheumatol* 2002;29:678-681.
14. Piscoya J, et al. Efficacy and safety of freeze-dried cat's claw in osteoarthritis of the knee: Mechanisms of action of the species *Uncaria guianensis*. *Inflamm Res* 2001;50:442-448.
15. Lamm S, et al. Persistent response to pneumococcal vaccine in individuals supplemented with a novel water soluble extract of *Uncaria tomentosa*, C-Med-100. *Phytomedicine* 2001;8:267-274.
16. Brinker F. Online Updates and Additions to *Herb Contraindications and Drug Interactions*. 3rd ed. Available at: www.eclecticherb.com/emp/updatesHCDI.html. Accessed Dec. 13, 2004.
17. Brinker F. *Herb Contraindications and Drug Interactions.* 3rd ed. Sandy, OR: Eclectic Medical Publications; 2001.
18. Hilepo JN, et al. Acute renal failure caused by 'cat's claw' herbal remedy in a patient with systemic lupus erythematosus. *Nephron* 1997;77:361.

Clinical Briefs

With Comments from Russell H. Greenfield, MD

Ayurvedic Products and Heavy Metals

Source: Saper RB, et al. Heavy metal content of ayurvedic herbal medicine products. *JAMA* 2004;292:2868-2873.

Goal: To determine the prevalence of heavy metals in Ayurvedic herbal remedies made in South Asia and sold in Boston-area stores.

Design: Systematic search strategy.

Setting: All stores selling Ayurvedic herbal medicine products from South Asia within a 20-mile radius of Boston City Hall.

Methods: All stores selling Ayurvedic remedies within the defined limits were identified by searching on-line Yellow Pages, an on-line directory of Indian grocery stores, a South Asia community business directory, and newspapers. Each store was visited and one package of all unique Ayurvedic botanical products offered for oral use was purchased (n = 70). Using X-ray fluorescence spectroscopy, concentrations of lead, mercury, and arsenic were determined for each product by the New England Regional Environmental Protection Agency (EPA). Using the manufacturers' dosage recommendations, estimated daily metal intake was compared with EPA safety standards. The authors returned to the stores at a later date and attempted to re-purchase each remedy initially found to contain heavy metals, as well as a randomly generated list of 14 products found to contain no heavy metals on initial testing.

Results: Heavy metals were found in 20% (14/70) of the Ayurvedic herbal medicine products (lead n = 13; mercury n = 6; and/or arsenic n = 6). All 10 repurchased products had heavy metal concentrations similar to that found in original samples. If ingested as directed, each product would have caused heavy metal intakes above the EPA regulatory standards. Of the 14 products selected for re-purchase that initially tested negative for heavy metals, none contained heavy metals in re-testing.

Conclusion: Users of Ayurvedic herbal medicine products from South Asia may be at risk for heavy metal toxicity.

Study strengths: Assessment of reproducibility; well-defined limits; generalizability (choosing only those products manufactured in South Asia).

Study weaknesses: Inability to identify chemical forms of the metals (which could impact degree of toxicity and bioavailability, most notably with mercury); lack of documentation of manufacturers' recommended duration of use of remedy.

Of note: Since 1978, at least 55 cases of heavy metal toxicity associated with Ayurvedic medicinal herbs have been published; the 70 products were manufactured by 26 Indian and one Pakistani company; seven of the 70 Ayurvedic remedies purchased specifically recommended use for children (six of which contained lead, three contained mercury, and three contained arsenic); Ayurvedic theory ascribes important therapeutic value to metals like mercury and lead, which are believed to be detoxified through heating and cooling, and the addition of specific herbs.

We knew that: It is estimated that 80% of India's population (1 billion people) uses Ayurvedic remedies; in one study of 22 herbal Ayurvedic products purchased in India, 64% contained lead and mercury, and 41% contained arsenic; lead toxicity from Ayurvedic herbal medicines has been tied to developmental delay, congenital paralysis and sensorineuronal deafness, fatal infant encephalopathy, and status epilepticus; concerns over heavy metal contamination also have been raised for traditional medicines from China, Malaysia, Mexico, and Africa; it is been estimated that 750,000 people in the United States have consulted with an Ayurvedic practitioner.

Clinical import: This well-done study raises significant concerns about the safety of Ayurvedic herbal remedies and reminds us that while issues exist with the standardization and regulation of Western medicinal herbs, the problems are compounded when considering botanicals manufactured outside the country. If Ayurvedic herbs are to be used, those manufactured in the United States should be recommended. Until safeguards are firmly established and in place, practitioners must include use of Ayurvedic herbal remedies produced in South Asia in the differential diagnosis of otherwise unexplained heavy metal toxicity.

What to do with this article: Keep a hard copy in your files and make copies for your peers. ❖

Supplement to *Alternative Medicine Alert*
February 2005

ALTERNATIVE MEDICINE ALERT™
A Clinician's Evidence-Based Guide to Alternative Therapies

Facts About Cancer Pain
Part 1: Managing and Treating Pain

HAVING CANCER DOES NOT ALWAYS MEAN HAVING PAIN. FOR THOSE WITH PAIN, THERE ARE many different kinds of medicines, ways to receive the medicine, and non-medicine methods that can relieve the pain you may have. You should not accept pain as a normal part of having cancer. When you are free of pain, you can sleep and eat better, enjoy the company of family and friends, and continue with your work and hobbies *(see Table 1)*.

Only you know how much pain you have. Telling your doctor and nurse when you have pain is important. Not only is pain easier to treat when you first have it, but pain can be an early warning sign of the side effects of the cancer or the cancer treatment. Together, you, your nurse, and your doctor can talk about how to treat your pain. You have a right to pain relief, and you should insist on it.

Cancer pain can almost always be relieved

There are many different medicines and methods available to control cancer pain. You should expect your doctor to seek all the information and resources necessary to make you as comfortable as possible. However, no one doctor can know everything about all medical problems. If you are in pain and your doctor suggests no other options, ask to see a pain specialist or have your doctor consult with a pain specialist. Pain specialists may be oncologists, anesthesiologists, neurologists, or neurosurgeons, other doctors, nurses, or pharmacists. A pain control team may also include psychologists and social workers.

If you have trouble locating a pain program or specialist, contact a cancer center, a hospice, or the oncology department at your local hospital or medical center. The National Cancer Institute's Cancer Information Service and other organizations can give you a list of pain management facilities. The American Cancer Society and other organizations may also be able to provide names of pain specialists, pain clinics, or programs in your area.

Controlling your cancer pain is part of the overall treatment for cancer

Your doctor wants and needs to hear about what works and what doesn't work for your pain. Knowing about the pain will help your doctor better understand how the cancer and the treatment are affecting your body. Discussions about pain will not distract your doctor from treating the cancer.

Preventing pain from starting or getting worse is the best way to control it

Pain is best relieved when treated early. You may hear some people refer to this as "staying on top" of the pain. Do not try to hold off as long as possible between doses. Pain may get worse if you wait, and it may take longer, or require larger doses, for your medicine to give you relief.

You have a right to ask for pain relief

Not everyone feels pain in the same way. There is no need to be "stoic" or "brave" if you have more pain than others with the same kind of cancer. In fact, as soon as you have any

Table 1
Effects of pain management

When pain is not treated properly, you may be:

- Tired
- Depressed
- Angry
- Worried
- Lonely
- Stressed

When cancer pain is managed properly, you can:

- Enjoy being active
- Sleep better
- Enjoy family and friends
- Improve your appetite
- Enjoy sexual intimacy
- Prevent depression

pain you should speak up. Telling the doctor or nurse about pain is not a sign of weakness. Remember, it is easier to control pain when it just starts rather than waiting until after it becomes severe.

People who take cancer pain medicines rarely become addicted to them

Addiction is a common fear of people taking pain medicine. Such fear may prevent people from taking the medicine. Or it may cause family members to encourage you to "hold off" as long as possible between doses. Addiction is defined by many medical societies as uncontrollable drug craving, seeking, and use. When opioids (also known as narcotics)—the strongest pain relievers available—are taken for pain, they rarely cause addiction as defined here. When you are ready to stop taking opioids, the doctor gradually lowers the amount of medicine you are taking. By the time you stop using them completely, the body has had time to adjust. Talk to your doctor, nurse, or pharmacist about how to use pain medicines safely and about any concerns you have about addiction.

Most people do not get "high" or lose control when they take cancer pain medicines as prescribed by the doctor.

Some pain medicines can cause you to feel sleepy when you first take them. This feeling usually goes away within a few days. Sometimes you become drowsy because, with the relief of the pain, you are now able to catch up on the much needed sleep you missed when you were in pain. On occasion, people get dizzy or feel confused when they take pain medicines. Tell your doctor or nurse if this happens to you. Changing your dose or type of medicine usually can solve the problem.

What is drug tolerance?

People who take opioids for pain sometimes find that over time they need to take larger doses. This may be due to an increase in the pain or the development of drug tolerance. Drug tolerance occurs when your body gets used to the medicine you are taking, and your medicine does not relieve the pain as well as it once did. Many people do not develop a tolerance to opioids. If tolerance does develop, usually small increases in the dose or a change in the kind of medicine will help relieve the pain.

Increasing the doses of opioids to relieve increasing pain or to overcome drug tolerance does *not* lead to addiction.

Side effects from medicines can be managed or often prevented

Some medicines can cause constipation, nausea and vomiting, or drowsiness. Your doctor or nurse can help you manage these side effects. These problems usually go away after a few days of taking the medicine. Many side effects can be managed by changing the medicine or the dose or times when the medicine is taken.

What are the different types of pain?

Pain may be acute or chronic. Acute pain is severe and lasts a relatively short time. It is usually a signal that body tissue is being injured in some way, and the pain generally disappears when the injury heals. Chronic or persistent pain may range from mild to severe, and it is present to some degree for long periods of time. Some people with chronic pain that is controlled by medicine can have breakthrough pain—this occurs when moderate-to-severe pain "breaks through" or is felt for a short time. It may occur several times a day, even when the proper dose of medicine is given.

What causes pain in people with cancer?

The pain you feel may be from the cancer itself. Whether you have pain and the amount of pain you have may depend on the type of cancer, the stage (extent) of the disease, and your pain threshold (tolerance for pain). Most of the pain comes when a tumor presses on bones, nerves, or body organs. It can also be caused by the treatment or procedures for diagnosing cancer. Or you may have pain that has nothing to do with your illness or treatment. Like anyone, you can get headaches, muscle strains, and other aches and pains.

How is cancer pain treated?

Cancer pain is usually treated with medicine (also called analgesics) and with non-drug treatments such as relaxation techniques, biofeedback, imagery, and others. Ask your doctor, nurse, or pharmacist for advice before

you take any medicine for pain. Medicines are safe when they are used properly. You can buy some effective pain relievers without a prescription or doctor's order. These medicines are also called nonprescription or over-the-counter pain relievers. For others, a prescription from your doctor is necessary.

For the small number of people for whom medicine and non-drug treatments do not work, other treatments are available: radiation therapy to shrink the tumor; surgery to remove part or all of the tumor; nerve blocks whereby pain medicine is injected into or around a nerve or into the spine to block the pain; and neurosurgery, where pain nerves are cut to relieve the pain.

Developing a plan for pain control

The first step in developing a plan is talking with your doctor, nurse, and pharmacist about your pain *(see Table 2)*. You need to be able to describe your pain to your health professionals as well as to your family or friends. You may want to have your family or friends help you talk to your health professionals about your pain control, especially if you are too tired or in too much pain to talk to them yourself.

Using a pain scale is helpful in describing how much pain you are feeling. Try to assign a number from 0 to 10 to your pain level. If you have no pain, use a 0. As the numbers get higher, they stand for pain that is getting worse. A 10 means the pain is as bad as it can be.

You may wish to use your own pain scale using numbers from 0 to 5 or even 0 to 100. Be sure to let others know what pain scale you are using and use the same scale each time, for example, "My pain is a 7 on a scale of 0 to 10."

You can use a rating scale to describe

- How bad your pain is at its worst
- How bad your pain is most of the time
- How bad your pain is at its least
- How your pain changes with treatment

Keeping track of details about the pain

You may find it helpful to keep a record or a diary to track the pain and what works best to ease it. You can share this record with those caring for you. This will help them figure out what method of pain control works best for you. Your records can include:

- Words to describe the pain.
- Any activity that seems to be affected by the pain or that increases or decreases the pain.
- Any activity that you cannot do because of the pain.
- The name and the dose of the pain medicine you are taking.
- The times you take pain medicine or use another pain-relief method.
- The number from your rating scale that describes your pain at the time you use a pain-relief measure.
- Pain rating 1-2 hours after the pain-relief method.
- How long the pain medicine works.
- Pain rating throughout the day to record your general comfort.
- How pain interferes with your normal activities, such as sleeping, eating, sexual activity, or working.
- Any pain-relief methods other than medicine you use such as rest, relaxation techniques, distraction, skin stimulation, or imagery.
- Any side effects that occur.

Table 2
Communicating with your caregivers

Tell your doctor, nurse, pharmacist and family or friends

- Where you feel pain
- What it feels like—sharp, dull, throbbing, steady
- How strong the pain feels
- How long it lasts
- What eases the pain, what makes the pain worse
- What medicines you are taking for the pain and how much relief you get from them

Your doctor, nurse, and pharmacist may also need to know

- What medicines you are taking now
- What pain medicines you have taken in the past, including what has worked and not worked
- Any known allergies

Questions to ask your doctor or nurse about pain medicine

- How much medicine should I take? How often?
- If my pain is not relieved, can I take more? If the dose should be increased, by how much?
- Should I call you before increasing the dose?
- What if I forget to take it or take it too late?
- Should I take my medicine with food?
- How much liquid should I drink with the medicine?
- How long does it take the medicine to start working?
- Is it safe to drink alcoholic beverages, drive, or operate machinery after I have taken pain medicine?
- What other medicines can I take with the pain medicine?
- What side effects from the medicine are possible and how can I prevent them?

What if I need to change my pain medicine?

If one medicine or treatment does not work, there is almost always another one that can be tried. Also, if a

schedule or way that you are taking medicine does not work for you, changes can be made. Talk to your doctor or nurse about finding the pain medicine or method that works best for you. You may need a different pain medicine, a combination of pain medicines, or a change in the dose of your pain medicines if:

- Your pain is not relieved.
- Your pain medicine does not start working within the time your doctor said it would.
- Your pain medicine does not work for the length of time your doctor said it would.
- You have breakthrough pain.
- You have side effects.
- You have serious side effects such as trouble breathing, dizziness, and rashes. Call your doctor right away if these occur. Side effects such as sleepiness, nausea, and itching usually go away after your body adjusts to the medication. Let your doctor know if these bother you.
- The schedule or the way you are taking the medicine does not work for you.
- Pain interferes with your normal activities, such as eating, sleeping, working, and sexual activity.

To help make the most of your pain control plan

- Take your pain medicine on a regular schedule (by the clock) to help prevent persistent or chronic pain.
- Do not skip doses of your scheduled medicine. Once you feel the pain, it is harder to control.
- If you experience breakthrough pain, use your short-acting medicine as your doctor suggests. Don't wait for the pain to get worse—if you do, it may be harder to control.
- Be sure only one doctor prescribes your pain medicine. If another doctor changes your medicine, the two doctors should discuss your treatment first.
- Never take someone else's medicine. Medicines that worked for you in the past or that helped a friend or relative may not be right for you.

Pain medicines affect different people in different ways. A very small dose may work for you, while someone else may need to take a much larger dose to obtain pain relief. Remember, your pain control plan can be changed at any time.

Medicines used to relieve pain

The type of medicine and the method by which the medicine is given depend on the type and cause of pain. For example, constant, persistent pain is best relieved by methods that deliver a steady dose of pain medicine over a long period of time, such as a patch that is filled with medicine and placed on the skin (skin patch) or slow-release oral tablets. Table 3 summarizes the types of medicines commonly used to relieve pain.

[Part 2 of this series, which will appear with the March issue of Alternative Medicine Alert*, will examine non-drug methods of pain relief.]*

Source: National Institutes of Health, National Cancer Institute. Available at: www.cancer.gov/cancertopics/paincontrol. Accessed Jan. 19, 2005.

Table 3

Types of medicines used to relieve pain

For Mild-to-Moderate Pain

Non-opioids: Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen. You can buy many of these over-the-counter (without a prescription). For others, you need a prescription. Check with your doctor before using these medicines. NSAIDs can slow blood clotting, especially if you are on chemotherapy.

For Moderate-to-Severe Pain

Opioids (also known as narcotics): Morphine, fentanyl, hydromorphone, oxycodone, and codeine. You need a prescription for these medicines. Non-opioids may be used along with opioids for moderate to severe pain.

For Breakthrough Pain

Rapid-Onset Opioids: Immediate-release oral morphine. You need a prescription for these medicines. A short-acting opioid, which relieves breakthrough pain quickly, needs to be used with a long-acting opioid for persistent pain.

For Tingling and Burning Pain

Antidepressants: Amitriptyline, nortriptyline, desipramine. You need a prescription for these medicines. Antidepressants are also prescribed to relieve some types of pain. Taking an antidepressant does not mean that you are depressed or have a mental illness.

Anticonvulsants (antiseizure medicines): Carbamazepine and phenytoin. You need a prescription for these medicines. Despite the name, anticonvulsants are used not only for convulsions, but also to control burning and tingling pain.

For Pain Caused by Swelling

Steroids: Prednisone, dexamethasone. A prescription is needed for these medicines. They are used to lessen swelling, which often causes pain.