AMERICAN HEALTH CONSULTANTS

ALTERNATIVE MEDICINE ALERT™

The Clinician's Evidence-Based Guide to Complementary Therapies

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

Reiki for Chronic Conditions: An Overview

By Nassim Assefi, MD

REIKI IS A FORM OF ENERGY MEDICINE DEVELOPED IN JAPAN IN the late 1800s. According to a vast body of primarily anecdotal literature, it is effective for improving pain and psychological well-being,[1-4] while appearing to have few, if any, adverse effects.[1,5] Reiki generally is delivered by a practitioner who lightly touches the patient (direct-contact Reiki). Or, Reiki is sent without physical contact with the patient (distant Reiki). With training, Reiki can be self-administered,[1] making it a low-cost, low-risk, patient-empowering intervention for chronic conditions.

Although there have been only two small randomized controlled trials of direct-contact Reiki for the treatment of pain and psychological symptoms published to date,[3,4] Reiki now is being offered in some hospitals, hospices, and psychotherapy practices in the United States.[1] The National Center for Complementary and Alternative Medicine (NCCAM), recognizing the increasing popularity of energy healing in the United States, recently sponsored studies of Reiki for the treatment of diabetic neuropathy and fibromyalgia.

History

Reiki is a Japanese word meaning universal life force. Reiki, like acupuncture, herbal therapies, qigong, and certain forms of massage, is a traditional Asian practice that emphasizes the body's balanced flow of *qi*, or vital energy.

Beyond oral history, little has been documented regarding the origins of Reiki. Dr. Mikao Usui, a Japanese monk and educator, is credited with the rediscovery of Reiki in the late 1800s while reading the original Tibetan Buddhist Sutras. The practice of Reiki was limited to Japan until 1935 when a Japanese-American woman, Hawayo Takata, imported Reiki to Hawaii. Takata's granddaughter, Phyllis Furumoto, founded the Reiki Alliance in 1983 and formalized the training of Reiki into three stages: Reiki I, Reiki II, and Reiki Master.

INSIDE

Training and Certification

Progression through each level involves successful completion of a short course, generally two days to one week in length, followed by practice. There are no prerequisites for Reiki I. Training involves learning the basic hand positions, studying Reiki's history, and receiving four "attunements" or energy transfers given by a Reiki Master. The Reiki II initiation is achieved at least three months after Reiki I, and includes instruction on focusing Reiki energy, and the delivery of Reiki from a distance. The Reiki Master level, which may be achieved after several years of Reiki practice, implies life-long devotion to healing and qualifies the practitioner to teach Reiki.

Currently, no certification process is required to practice Reiki in the United States, nor is there an objective measure that determines who can progress to Reiki Master. The International Center for Reiki Training reports the initiation of about 100,000 Reiki practitioners since the 1980s.[6]

Application and Techniques

Direct-contact Reiki between a practitioner of any level and a patient is the most common form of Reiki delivery. This treatment typically is administered with the recipient fully clothed on a treatment table while the practitioner lightly touches designated positions for two to five minutes each. Some patients report deep relaxation during treatment, while others feel more subtle sensations like heat, cold, or tingling. Full treatments may last from 30-90 minutes, although not all positions are necessarily touched during a given Reiki treatment.

There are 13 standard hand positions in direct-contact Reiki—three on the head and neck, four on the thorax and abdomen, and six on the back *(see Figure)*. Depending on the Reiki Master, these may be sub-divided into as many as 15-18 areas.[7] The basic positions are hypothesized to correlate with the body's chakras, meridians, or energy centers. However, many Reiki Masters believe that placement of their hands on any part of body (on so-called auxiliary positions) will result in some therapeutic benefit.[7]

Distant Reiki purportedly can be delivered in the patient's presence (i.e., across the room) or from great distances (i.e., across continents). Distant Reiki is taught at the Reiki II level and is optimally administered by Reiki Masters.

Allopathic health care providers have popularized the use of brief Reiki treatments, such as the touching which may naturally occur between a primary care provider and patient during the course of a physical examination.[1,2] Reiki also can be self-administered, which both reduces the cost of treating chronic conditions and enhances patients' sense of self-esteem and control over their symptoms.

Mechanism of Action

To date, there is no biomedical explanation for the reported beneficial effects of Reiki, although many theories such as bioelectromagnetic field emission from human touch or intention to heal have been proposed. If Reiki is shown to be effective in well-controlled, randomized clinical trials, an important step in unraveling its mechanism will be to distinguish it from nonspecific, placebo effects (i.e., separate from attention, compassionate caring, relaxation response, and expectation). Furthermore, direct-contact Reiki can be studied separately from distant Reiki.

Reported Uses

In the United States, Reiki typically has been used in conjunction with Western-based therapies. Unlike homeopathy, which discourages the use of Western therapeutic modalities, Reiki can be easily integrated with allopathic approaches. It is used in the treatment of pain, palliative care, wound healing, amelioration of depression and anxiety, and spiritual well-being.[1,2,8-10]

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by 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: $45 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@ahcpub.com
Editorial E-Mail: paula.cousins@ahcpub.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
$319 per year (Student/Resident rate: $145).
Multiple Copies
1-9 additional copies: $242 each; 10 or more copies: $215 each
Outside the United States
$349 per year plus GST (Student/Resident rate: $160 plus GST).

Accreditation

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

American Health Consultants designates this continuing medical education activity for up to 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 educational activity.

This CME activity was planned and produced in accordance with the ACCME Essentials.

Alternative Medicine Alert has been approved by the American Academy of Family Physicians as having educational content acceptable for Elective credit hours. Term of approval covers issues published within one year from the beginning distribution date of July 1, 2005. This volume has been approved for up to 24 Prescribed credit hours. Credit may be claimed for one year from the date of this issue.
For CME credit, add $50.

Questions & Comments

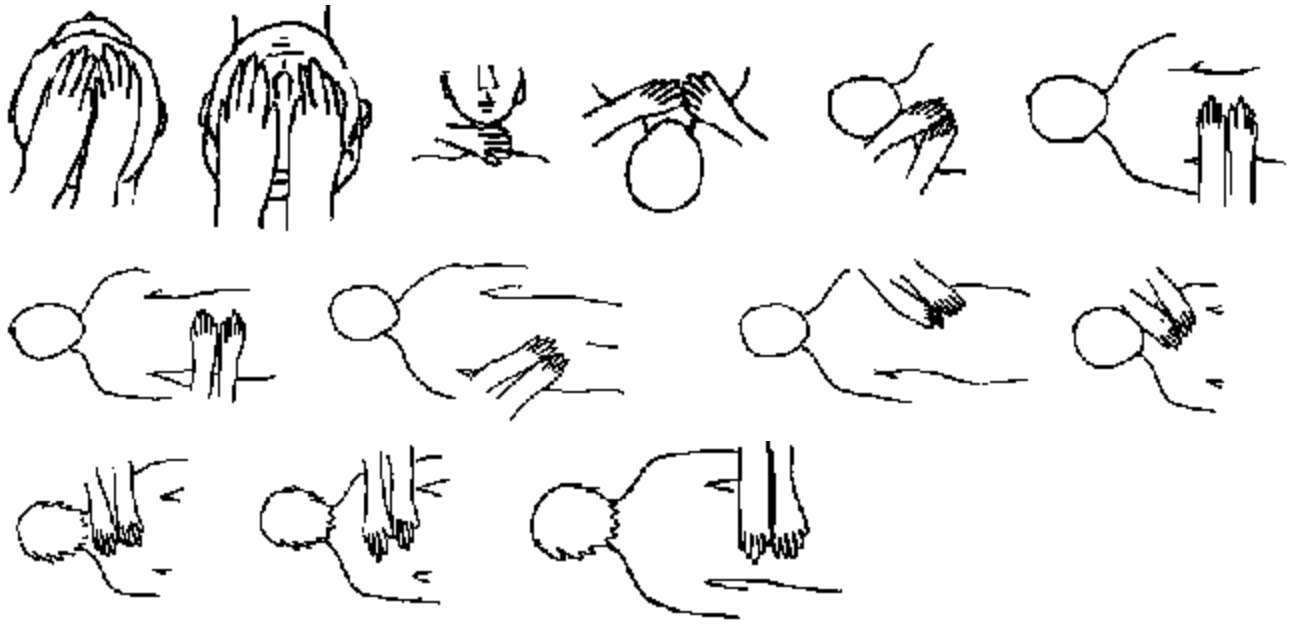
Please call **Paula Cousins,** Managing Editor, at (816) 960-3730 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

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. Assefi, Dr. Balk, Dr. Cirigliano, Dr. deLeon, Dr. Gaster, Dr. Ramalanjaona, Dr. Schiedermayer, Dr. Sorrentino, Dr. Spar, and Dr. Udani have no relationships with companies related to the field of study covered by this CME program. Dr. Barrette is an advisor for NaturalStandard.com. Dr. La Puma is Director of Research and Education at CHEFClinic Nutritional Medical Corp and President of Meeting Meals.

Figure

Traditional Reiki hand positions



Key: (from left to right, beginning with top row) crown chakra; third eye chakra; throat chakra; heart center; heart chakra, right side; solar plexus chakra, lower abdomen chakra; root chakra, right side; root chakra, left side; heart chakra, left side; upper back, middle back; lower back.

Physiological Studies

Although anecdotal case reports abound, there is a paucity of high-quality scientific literature on Reiki. Two non-randomized, poorly controlled studies in heterogeneous populations have documented physiological changes in patients receiving Reiki.

One study of hemoglobin levels in 48 non-anemic adults before and after Reiki I training compared to a control group of 10 medical professionals showed that almost 60% of those receiving Reiki but none of the medical professionals increased their hemoglobin concentrations.[11]

Another study that attempted to document the relaxation response following a single 30-minute Reiki treatment in 23 patients found increased salivary IgA levels and decreased systolic blood pressure compared to baseline values, but no change in salivary cortisol, peripheral temperature, and EMG-determined muscle tension.[12]

Finally, a randomized, double-blinded, crossover study compared electrolytes and blood sugar concentrations before, during, and after administration of a combination of Reiki, LeShan (a form of psychic healing), Therapeutic Touch, and qigong therapies in 14 patients; various control conditions were utilized.[13] Glucose levels were slightly but significantly different in the patients receiving the combination treatment than the control treatment. However, there was no adjustment for or record of dietary intake and no assessment of blinding, and Reiki was not studied in isolation from the other energy therapies.

Clinical Trials

A comprehensive literature search using PUBMED, PsychLIT, EMBASE, CINAHL, BIOSIS, and the Cochrane Library revealed only two clinical efficacy trials of direct-contact Reiki.

A 1997 study in 20 volunteers experiencing pain from a variety of conditions used Likert and visual analogue scales (VAS) to compare pain before and after a single Reiki treatment.[4] Although more than 85% of patients reported significantly improved pain scores following Reiki, these results could be attributed to a placebo effect since a control group was not examined.

A second study randomized 120 patients with diverse chronically painful conditions to 30-minute bi-weekly sessions of Reiki, sham Reiki, progressive muscle relaxation, and magazine reading in a doctor's office.[14] Symptoms were measured by validated scales at three time points: a pre-intervention baseline, at the end of the five-week trial, and three months post-trial. The true Reiki group had significant improvements in pain control, depression, anxiety, and self-esteem compared to the three control groups. However, patient blinding was problematic.

It is unlikely that patients in the latter two groups believed they were receiving Reiki. Furthermore, while sham and true Reiki practitioners touched patients in identical locations, many details—such the practitioners' manner of introduction, their comfort in touching patients, their way of answering questions, and non-verbal cues—may have revealed the true status of the practitioner to the patients.[15]

No clinical trials could be identified that examine distant Reiki interventions alone. However, a single randomized double-blinded crossover trial of distant Reiki combined with LeShan healing in which the patients reportedly could not see the healers demonstrated significant improvement in pain control following extraction of impacted lower third molar teeth.[16] Two separate operations were performed in 21 patients with bilateral asymptomatic impacted third molars. The first was followed in three hours by either 15-20 minutes of distant Reiki and LeShan or no distant healing; after the second operation, subjects who initially received placebo were assigned to the intervention arm, and vice versa. Although pain relief was significantly improved in the distant healing group up to 4-9 hours postoperatively, the placebo effect cannot be ruled out because blinding to treatment was not assessed and objective measures of pain (i.e., heart rate or analgesic use) were not obtained to confirm the subjective reports.

Conclusion

Applying the paradigm of randomized, double-blinded, placebo-controlled trials, the gold standard for biomedically based interventions, is quite challenging in Reiki and all other energy medicine studies. Because there is no widely accepted mechanism for Reiki's biologic plausibility, it is difficult to design a placebo that mimics Reiki without inadvertently delivering an active therapy. Furthermore, although successfully blinding patients to the nature of the energy treatment they are receiving is difficult, blinding practitioners to the kind of treatment they are delivering is nearly impossible.

Nevertheless, Reiki offers another possibility for adjunctive therapy without a risk of doing harm. If carefully controlled ongoing and future studies of Reiki show benefit over placebo, they will help validate claims about the beneficial effects of Reiki and other forms of energy medicine, while making conventionally trained physicians pause about the complex nature of the healing process.

Recommendation

Reiki can be recommended as a low-risk, but unproven, adjunctive therapy for pain and psychological symptoms in those who have failed conventional therapies. ❖

Dr. Assefi is Attending (Clinician-Teacher), Departments of Medicine and Obstetrics/Gynecology, Complementary and Alternative Medicine Liaison, School of Medicine, University of Washington in Seattle.

References

1. Barnett L, Chambers M. *Reiki Energy Medicine.* Rochester, VT: Healing Arts Press; 1996.
2. Eos N. *Reiki and Medicine.* Grass Lake, MI; 1995.
3. Dressen L. *Reiki: An Ancient System of Natural Healing, First-Degree Training Manual.* Abilene, TX: Sky Dancer Press; 1996.
4. Olson K, Hanson J. Using Reiki to manage pain: A preliminary report. *Cancer Prev Control* 1997;1: 108-113.
5. Stewart JC. *Reiki Touch: The Essential Handbook.* Atlanta, GA: The New Leaf Distributing Company; 1995.
6. Benor D. Doctor-healer Network: http://wholistichealingresearch.com/consultations/dhnna4-25.html; 2001.
7. Young NJ, Reiki Master and Reiki Elder of Washington State. Center of Origins Clinic: Personal Communication; 2001.
8. Bullock M. Reiki: A complementary therapy for life. *Am J Hosp Palliat Care* 1997;14:31-33.
9. Sawyer J. The first Reiki practitioner in our OR. *AORN J* 1998;67:674-677.
10. Sharon E, et al. Energy dissipation in dynamic fracture. *Phys Rev Lett* 1996;76:2117-2120.
11. Wetzel W. Reiki healing: A physiologic perspective. *J Holistic Nurs* 1989;7:47-54.
12. Wardell DW, Engebretson J. Biological correlates of Reiki touch healing. Issues and innovations in nursing practice. *J Adv Nursing* 2001;33:439-445.
13. Wirth D, et al. Wound healing an complementary therapies: A review. *J Altern Complement Med* 1996; 4:493-502.
14. Dressen L, Singg S. Effects of Reiki on pain and selected affective and personality variables of chronically ill patients. *Subtle Energies Energy Med* 2000;9:51-81.
15. Mansour AA, et al. A study to test the effectiveness of placebo Reiki standardization procedures developed for a planned Reiki efficacy study. *J Altern Complement Med* 1999;5:153-164.
16. Wirth DP, et al. The effect of complementary healing therapy on postoperative pain after surgical removal of impacted third molar teeth. *Complement Ther Med* 1993;3:133-138.

Natural Immunomodulators for the Treatment of Cancer

By Jay Udani, MD, and Myles Spar, MD, MPH

MANY CANCERS, ESPECIALLY LYMPHOMAS AND LEUKEmias, may be related to a lack of normal immune system function. Persons with disorders of immunity have an increased likelihood of being diagnosed with cancer, and those with congenital immunodeficiencies develop cancers at 200 times the expected prevalence.[1]

The medical use and adverse effects of accepted immunomodulators (e.g., human cytokines such as interferons and interleukins) are well known: Unfortunately, they can be a cause of significant toxicity and can induce rapid development of resistance. Resistance to immunomodulatory herbs and fungi has not yet been observed, and several herbs and fungi have been shown to have immunomodulatory activity (i.e., they boost the ability of the immune system to fight cancer, primarily through improved activity of natural killer [NK] cells).

Background: The Immune System

The immune system can be separated into two divisions: specific and innate immunity. Specific immunity involves the specific identification of a foreign antigen and the organization of an attack against it by cells designed specifically for that individual target molecule. Innate immunity involves general surveillance by immune system cells designed to take out any molecules that appear foreign, even if they haven't been specifically identified.

Both divisions are driven primarily by white blood cells. T-cells and B-cells are those white blood cells that are stimulated chiefly by specific foreign antigens, and are thus the main components of specific immunity. NK cells are types of white blood cells that are neither T-cells nor B-cells. They are the chief components of innate immunity and their role is in immune surveillance and in mediating natural resistance against tumors.

NK cells are found throughout the body and do not require a specific antigen-mediated activation. They can attack foreign or cancer cells directly without prior sensitization, unlike T-cells and B-cells, which recognize a foreign antigen through a receptor found on the antigen that specifically identifies that cell, almost like a nametag. Although most foreign cells have these receptors, many cancer cells lack such a receptor, enabling them to evade surveillance by T-cells and B-cells.

Innate Immunity and Cancer

NK cells destroy cancer cells by binding to a different, more general receptor on the cancer cell and releasing toxic granules into the cell. Cancer cells are able to defend themselves against such attack by ingesting the NK cell whole or by releasing immune-suppressive substances.[2,3] There has been interest in the use of NK cells for treatment of cancers once they develop. NK cell activity—the avidity with which they recognize and bind to tumor cells—is the most important measure of their function.

Mechanisms of Action

In addition to direct cytotoxic activity against tumor cells, activated NK cells also produce a variety of cytokines, which in turn have direct anticancer cell activities and immunoregulatory effects, such as up-regulation of T-cells and B-cells and further activation of NK cells. Immunomodulators that enhance NK cell activity can stimulate production of interferon-gamma and tumor-necrosis factor-alpha.[4]

In human trials, NK cell activity has been shown to be depressed among patients with many different malignancies. A decrease in NK cell activity has been noted before relapse in leukemia, in breast cancer patients with regional metastases to lymph nodes, and in lymphoma.[5] There is a positive correlation between NK cell activity and survival time in patients with solid tumors without metastases.[6]

Clinical and Laboratory Studies

Immunomodulators discussed here include astralgus, MGN-3™, and inositol hexaphosphate (IP6). Not all of these have been proven to be useful in cancer specifically, but all have shown some ability to improve immune function.

Astralgus

Astralgus (*Astralgus membranaceus*), also known as huang qi, has been used in China for more than 2,000 years. In Chinese medicine, astralgus is meant to increase the circulation of wei-chee (a protective energy) around the body. It also is used to be protect against the six primary causes of disease, the "Six Evils."[7]

In laboratory studies, astralgus has been shown to exert antitumor effects in murine models of renal cell carcinoma while enhancing lymphokine-activated killer cells.[8]

In one Chinese clinical study, astralgus and ginseng were added to traditional chemotherapy in the treatment of small cell lung cancer. The group showed improved survival rates over conventional treatment, with a gain in

Table

Abstracted data: "Natural" immunomodulators

Immunomodulator	Recommended Dose	Mechanism of Immunomodulation
Astralgus	1,000 mg tid of dried herb; or 9-15 g made into tea	• Activation of macrophages • IL-2 activity • Potentiation of IFN activity
MGN-3	15-45 mg/kg/d	• Enhanced NK cell activity • TNF-alpha induction
IP6	800 mg bid	• Enhanced NK cell activity

survival of 3-17 years.[9] One Chinese study evaluated the effect of astralgus preparations in 115 cases of chemotherapy-induced leukopenia. Two concentrations of astralgus were used, 5 g and 15 g twice daily of a Chinese formulation. Both groups showed improvement in white blood cell counts with the higher concentration having a significantly stronger effect.[10] Neither Chinese study has been replicated in the West.

MGN-3

MGN-3 is an arabinoxylan extracted from rice bran that is produced by hydrolyzing rice bran using enzymes from mycelia of Shiitake, Kawaratake, and Suehirotake mushrooms. It is a polysaccharide that contains (-1,4 xylopyronase hemicellulose). MGN-3 has shown improvement in NK cell activity in vitro and in vivo.

In a series of studies available only as abstracts or in abbreviated form, Ghoneum et al showed an improvement in NK activity following treatment with MGN-3 in a group of 32 cancer patients, all of whom exhibited lower than normal NK cell function at study outset.[11]

Ghoneum also examined the effect of MGN-3 on NK cell activity in a series of 24 individuals using 15-45 mg/kg/d for two months. NK activity was enhanced at all concentrations used and acted in a dose-dependent fashion to increase NK cell activity significantly over the duration of the study.[12]

Ghoneum et al also found baseline NK cell activity to be low in patients with varied advanced cancers: MGN-3 led to a significant increase in NK cell activity after 1-2 weeks and was reportedly sustained for up to five years with continued administration.[13] A decrease in tumor markers and long-term stabilization of disease also were reported, though again, only through abstracted or abbreviated publication.

MGN-3 has been shown to decrease the toxicity of standard chemotherapy in animal studies. Rats receiving MGN-3 in addition to chemotherapy (doxorubicin or cisplatin) showed significant weight gain and decreased gastrointestinal pathology, and even a decreased death rate, as compared to those receiving the chemotherapy alone.[14] Uyemura et al showed a direct effect of MGN-3 on tumor cell growth and cytokine production (IL-10 and IL-12) in patients with breast cancer.[15] No other human studies could be identified.

Inosital hexaphosphate (IP6)

IP6 is found in cereals and legumes, particularly in the bran of mature seeds. It is the major phosphorous storage compound of plants, comprising 1-7% of the dry weight of most cereals, nuts, and legumes.[16] IP6 also is endogenous to most mammalian cells in smaller amounts.[17] Cellular functions include signal transduction and cellular proliferation and differentiation.

Inositol hexaphosphate has shown anticancer activity in breast, colon, liver, and prostate cells and experimental tumors.[18,19] One study by Shamsuddin showed a marked inhibition of tumor development in mice given IP6 vs. controls.[20] The mechanism of action is thought to be via immunomodulation with upregulation of tumor suppressor genes. IP6 is available as a supplement in combination with inositol. Studies in humans using IP6 in cancer treatment are ongoing; however, no clinical trials in humans showing anticancer activity of IP6 have been published to date.

Adverse Effects

Astralgus may lower blood pressure or cause diuresis and potentially may cause an interaction with opiates. In Chinese medicine, astralgus usually is combined with other herbs, depending on the individual's specific condition. Therefore, it is difficult to separate out any untoward effects from astralgus in clinical use.

In human trials using up to 45 mg/kg/d of MGN-3 for six months, there have been no reported abnormalities in blood chemistries or liver enzymes. There were no reports of side effects or interactions with other medications used.[21] In animal studies, MGN-3 has shown no toxic effects in doses up to 36 g/kg. A review of the literature on MGN-3 reveals no published adverse effects.

IP6 may interfere with absorption of minerals in the stomach; therefore, it should be taken on an empty stomach. There is a concern that use of IP6 with drugs that affect platelet aggregation may increase the risk of bleeding because in vitro IP6 can inhibit platelet aggregation. This effect has not been demonstrated in humans. Because of a lack of human clinical trials, the possible adverse effects of IP6 have not been fully presented. However there have been no reports of any side effects.

Conclusion

There is an ongoing search for substances that can be used to treat cancer by utilizing the body's own natural anticancer mechanisms. Substances that can augment innate immunity involving NK cells hold much promise.

The substances discussed here have been shown to modulate the immune system, primarily through improving NK cell activity, which is closely related to control of malignancies. Improved control helps to decrease tumor burden, which theoretically may improve local control, survival, and cancer- and treatment-related toxicity. Minimal side effects have been associated, thus far, with these substances.

Although none of these plant or fungus-based substances has been shown to be magic bullets for cancer as stand alone treatments, they all show promise as adjuncts to conventional therapy, by mitigating toxic side effects (in the case of MGN-3) and by boosting the body's innate immunity.

The greatest weight of evidence, although largely in vitro, seems to favor the use of MGN-3 as adjunctive treatment for malignancy and the use of astralgus as immune support during chemotherapy when the patient has leukopenia.

Recommendation

Although the evidence for clinical use of the immunomodulators discussed here is still scant, there seems to be growing support for their use as an adjunct to cancer treatment. Astralgus would be beneficial in those undergoing chemotherapy who develop leukopenia. MGN-3 would be recommended as an adjunct to traditional cancer therapy, especially for those with lymphomas and leukemia, given the importance of natural killer cells in these malignancies. IP6 would not be recommended currently given the lack of clinical evidence in combination with its potential impact on coagulation. ❖

Dr. Udani and Dr. Spar are Clinical Instructors, University of California Los Angeles School of Medicine; Dr. Udani also is Medical Director, Northridge Hospital Integrative Medicine Program, Northridge, CA.

References

1. Whiteside TL, Herberman RB. Human natural killer cells in health and disease. *Clin Immunotherapeutics* 1994;1:56-66.
2. Cotran RS, et al. Natural Killer Cells. In: Cotran RS, et al, eds. *Robbins Pathologic Basis of Disease.* 5th ed. Philadelphia, PA: WB Saunders; 1994;191-193.
3. Vodjani A et al. Possible role of natural killer cells in host resistance against tumors and diseases. *Clin Immunol Allergy* 1983;3:479-485.
4. Ghoneum M, Jewett A. Production of tumor necrosis factor-alpha and interferon-gamma from human peripheral blood lymphocytes by MGN-3, a modified arabinoxylan from rice bran, and its synergy with interleukin-2 in vitro. *Cancer Detect Prev* 2000;24: 314-324.
5. Lee GR, et al. NK Cells and Malignancies. In: *Wintrobe's Clinical Hematology.* 10th ed. Baltimore, MD: Lippincott Williams and Wilkins; 1999:530-545.
6. Vodjani A. *Natural Killer Cytotoxicity, Apoptosis and Cell Cycle in Human Health and Diseases.* Beverly Hills, CA: Immunosciences Lab, Inc.; 1997:16.
7. Reid A. A *Handbook of Chinese Healing Herbs.* Boston, MA: Shambhala Publications; 1995.
8. Lau BH, et al. Chinese medicinal herbs inhibit growth of murine renal cell carcinoma. *Cancer Biother* 1994; 9:153-161.
9. Cha RJ, et al. Non-surgical treatment of small cell lung cancer with chemo-radio-immunotherapy and traditional chinese medicine. *Chung Hua Nei Ko Tsa Chih* 1994;33:462-466.
10. Weng XS. Treatment of leukopenia with pure astralgus preparation—an analysis of 115 leukopenic cases [in Chinese]. *Chung Kuo Chung Hsi I Chieh Ho Tsa Chih* 1995;15:464-464.
11. Ghoneum M, et al. NK Immunorestoration of cancer patients by MGN-3, a modified arabinoxylan rice bran, Available at: www.publishedresearch.com. Accessed Sept. 3, 2002.
12. Ghoneum M. Enhancement of human natural killer cell activity by modified arabinoxylane rice bran (MGN-3). *Int J Immunother* 1998;IV:197.
13. Ghoneum M, Manatalla G. NK immunomodulatory function in 27 patients by MGN-3, a modified arabinoxylane from rice bran. Abstract, 87th Annual Meeting of the American Association for Cancer Research; Washington, DC; April 1996.

14. Jacoby HI, et al. The effect of MGN-3 on cisplatin and adriamycin induced cytotoxicity in the rat. *Gastroenterology* 2000;April(Suppl):15-19.
15. Uyemura, Koichi et al. MGN-3, a novel antitumor agent. Available at: www.publishedresearch.com. Accessed Sept. 3, 2002.
16. Graf E, Eaton JW. Antioxidant functions of phytic acid. *Free Radic Biol Med* 1990;8:61-69.
17. Shamsuddin AM, et al. IP6: A novel anti-cancer agent. *Life Sci* 1997;61:343-354.
18. Challa A, et al. Interactive suppression of aberrant crypt foci induced by azoxymethane in rat colon by phytic acid and green tea. *Carcinogenesis* 1997;18: 2023-2026.
19. Thompson LU, Zhang L. Phytic acid and minerals: Effect on early markers of risk for mammary and colon carcinogenesis. *Carcinogenesis* 1991;12:2041-2045.
20. Shamsuddin AM, Vucenik I. Mammary tumor inhibition by IP6: A review. *Anticancer Res* 1999;19(5A): 3671-3674.
21. Ghoneum M. Effects of MGN-3 on human natural killer cell activity and interferon-gamma synthesis in vivo. *FASEB J* 1996;10:26-32.

Huperizine A for the Treatment of Alzheimer's Disease

By Georges Ramalanjaona, MD, DSc, FACEP, MBA

ALZHEIMER'S DISEASE (AD) IS THE MOST COMMON AGE-related dementia in U.S. adults, affecting up to 5% of the population older than age 65.[1] It is characterized by progressive neurodegenerative impairment of the central nervous system (CNS) and diminished cholinergic neurotransmission. Therefore, present therapeutic strategy focuses on enhancing cholinergic activity in the CNS using acetylcholinesterase inhibitors (ACHIs) to improve cognitive deficits. However, current FDA-approved drugs, such as tacrine and donepezil, display significant side effects, including cholinergic effects and hepatotoxicity.[2]

Huperizine A (Hup A), a natural lycopodium alkaloid isolated from the Chinese herb *Hypersia serrata*, is a potent, centrally active, and selective ACHI and has been shown to improve cognitive impairment in various animal and human brain function models.[3-5]

The purpose of this article is to review the current clinical evidence on the role of Hup A in AD. Clinical trials suggest that Hup A may enhance short-term memory and mental status in AD patients.

Pharmacokinetics

In animal studies, purified Hup A displays a high oral bioavailability, good intestinal absorption, and an excellent penetration through the blood-brain barrier. It has a long half-life in vivo, and a longer duration of effects on acetylcholinesterase (ACHE) (3 hours) than tacrine (2 hours) and physostigmine (30 minutes).[6]

Mechanism of Action

Hup A acts on AD by several mechanisms:

Hup A is a reversible and selective ACHI that prevents the degradation of endogenous acetylcholine (ACH), a neurotransmitter involved in memory formation and neuronal communication.[7] Brain biopsies of patients with AD have shown significant loss of presynaptic cholinergic neurons.[8] Hup A appears to bind more tightly, specifically, and longer to the brain ACH than the other ACHIs. Thus, the ACHE-Hup A complex has a slower dissociative rate and more effective therapeutic index compared to other drugs.

Studies using cultures of cells derived from hippocampus and cerebellum of rat embryos have pointed out that Hup A decreases neuronal cell death induced by toxic levels of glutamate. This compound activates N-Methyl-D aspartate (NMDA) receptors and increases the flux of calcium ions into the neurons, which is neurotoxic.[9]

Excessive deposition of amyloid B-Peptide (AB) in the brain is the major pathological hallmark of AD. Hup A acts as a neuroprotective agent against AB-induced oxidative injury resulting from free radicals.[10]

Clinical Studies

Although clinical trials demonstrating the role of Hup A in AD are scarce, their results are clinically significant and deserve our attention *(see Table)*.

In a prospective, double-blind, placebo-controlled study of 103 patients in China (evidence grade I in class I-III), Xu et al showed a statistically significant improvement ($P < 0.01$) in memory and behavioral and cognitive function in 58% of AD patients taking 200 mcg/d of Hup A compared to 36% of placebo-group patients during the eight-week period.[11] Memory, cognitive function, and behavioral functions were measured by memory quotient, Mini-Mental State Examination scale, and activity of daily living scale, respectively. There was a slight increase in mild peripheral cholinergic side effects in the Hup A group compared to the placebo group. However, there was no statistically significant difference between those two groups.

In a more recent trial, Xu et al used a prospective multicenter, double-blind, randomized parallel study of

Table

Recent randomized clinical trials of Huperizine A in the treatment of Alzheimer's disease

Studies	Patients	Treatment	Duration	Results
Xu et al (1995)[11]	103	Hup A vs. placebo	8 weeks	Hup A group significantly improved in all three categories vs. placebo
Xu et al (1999)[4]	60	Hup A in tablets and capsules vs. placebo	8 weeks	No difference between Hup A tablet and capsule Statistically significant in all psychological evaluation before and after the six-day Hup A treatment ($P < 0.01$)
Mazurek et al (unpublished reports)	29	Hup A group	ongoing	Preliminary results show improvement in mental status in 50% of Hup A group.

60 patients (evidence grade I) to show a clinically and statistically significant difference ($P < 0.01$) on all psychological tests before and after the 60-day trial of Hup A for the two treatment groups (four tablets or four capsules a day of 50 mcg).[12] However, there was no significant difference between the two Hup A groups or the two placebo groups, and no clinically significant side effects in either group.

Limitations of these clinical trials include small sample size, lack of longer-term follow up, and absence of direct clinical comparison with other ACHI.

Ongoing Clinical Trials

In a preliminary study of 29 AD patients, Mazurek showed a marked improvement in mental status in more than 50% of patients taking 100 mcg/d of Hup A (unpublished reports, limited data). This preliminary trial seems promising in symptomatic improvement of AD; final results are still pending and unpublished.

Adverse Effects

In short-term trials, a slight increase in mild peripheral cholinergic side effects, such as nausea, vomiting, and diarrhea, have been reported in Hup A groups.[13] These side effects are not statistically significant compared to placebo.

Contraindications and Precautions

To date, there are no reported contraindications or drug interactions of Hup A in human clinical trials. Because of insufficient reliable data, pregnant and nursing women should avoid Hup A use. No interactions are known to occur with foods or laboratory tests. Theoretically, concurrent use of anticholinergic drugs might decrease the effectiveness Hup A. Conversely, cholinergic drugs and ACHI might increase Hup A effects.

Formulation and Dosage

Hup A was first synthesized in 1991, and is commercially marketed in the United States as Cerebra in the form of dietary supplements.

In China, it has been approved as a prescription drug for symptomatic treatment of AD.

Current dosage used in clinical trials ranges from 100 to 200 mcg/d PO in divided doses.

Conclusion

Preliminary short-term studies are promising on the role of Hup A in the symptomatic treatment of AD. Specifically, patients treated with Hup A showed significant improvement in their memory and cognitive and behavioral function. Based on current trials, Hup A is possibly effective and safe in improving short-term memory and mental status in AD. Application of these results is limited due to small sample size and lack of long-term follow up.

Recommendation

Based on the scientific limitations of the data, Hup A cannot yet be recommended in AD patients. Final recommendations are awaiting the results of long-term (five-year), large clinical trials to confirm the effectiveness and safety of Hup A in AD patients. ❖

Dr. Ramalanjaona is Associate Chairman for Academic Affairs, Department of Emergency Medicine, Seton Hall University, School of Graduate Medical Education, South Orange, NJ; and Director of Research, Division of Emergency Medicine, St. Michael's Hospital, Newark, NJ.

References

1. Hardy J, et al. Transmitted deficits in Alzheimer's disease. *Neurochem Int* 1985;7:545-563.

2. Knapp MJ, et al. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group *JAMA* 1994;271: 985-991.
3. Jia WY, et al. Improving effects of Huperizine A on spacial working memory in aged monkeys and young adult monkeys with experimental cognitive impairment. *J Pharm Exp Ther* 1999;288:814-819.
4. Xu SS, et al. Huperizine A in capsules and tablets for treating patients with Alzheimer's disease. *Zhongguo Yao Li Xue Bao* 1999;20:486-490.
5. Zhang SL. Therapeutic effects of Hup A on the aged with memory impairment. *N Drug Clin Remedies* 1986;5:260-262.
6. Cheng DH, Tang XC. Comparative studies of Huperizine A, E2020 and tacrine on behavior and cholinesterase activities. *Pharm Biochem Behav* 1998;60:377-386.
7. Kozikowski AP, et al. Synthesis of Huperizine A and its analogues, and their anti-cholinesterase activity. *J Org Clem* 1991;56:4636-4645.
8. Skolnick AA. Old Chinese herbal medicine used for fever yields possible new Alzheimer disease therapy. *JAMA* 1997;277:776.
9. Gordon RK, et al. A Hup A interacts with the NMDA receptor ion channel. *FASEB J* 1997;11:A903.
10. Ved HS, et al. Huperizine A, a potential therapeutic agent for dementia, reduces neuronal cell death caused by glutamate. *Neuroreport* 1997;8:963-968.
11. Xu SS, et al. Efficacy of tablet Huperizine A on memory, cognition, and behavior in Alzheimer's disease. *Acta Pharm Sin* 1995;16:391-395.
12. Xu SS, et al. Efficacy of tablet Huperizine A on memory and cognition in patients with benign senescent forgetfulness. *Chin J Clin Pharm Ther* 1997;2:1-4.
13. Bai DL, et al. Huperizine A, a potential therapeutic agent for treatment of Alzheimer's disease. *Curr Med Chem* 2000;7:355-374.

CME Questions

21. Reiki can be delivered:
a. by light touch.
b. by sending energy without touching the patient.
c. from the patient to him/herself.
d. from great distances.
e. All of the above

22. Reiki purportedly is useful for:
a. pain.
b. depression.
c. anxiety.
d. All of the above

23. Which of the following is *not* true regarding Reiki?
a. It most often is administered by touching standard positions while the patient is fully clothed on a treatment table.
b. There are no known reported adverse effects.
c. Reiki requires a licensure to administer.
d. There are no clinical trials of distant Reiki healing alone.
e. Conducting randomized, double-blinded placebo-controlled trials of Reiki is challenging.

24. Lymphomas and leukemias can represent an immune system failure.
a. True
b. False

25. Which one of the following has *not* been shown to have adverse effects?
a. MGN-3
b. IP6
c. Prednisone
d. Astralgus

26. One of the most common mechanisms of immunomodulation among the substances used to help fight cancer is:
a. enhancement of Natural Killer cell activity.
b. decreasing Natural Killer cell activity.
c. enhancing antigen-specific B-cell activity.

27. Astralgus has been shown to improve cancer treatment by:
a. killing cancer cells directly.
b. elevating white blood cell counts in cases of leukopenia.
c. minimizing nausea from chemotherapy.
d. helping hair grow back faster after chemotherapy.

28. Compared to tacrine and physostigmine, Huperizine A is:
a. derived from a Chinese herb.
b. incompletely tested.
c. available over the counter.
d. All of the above

29. Current clinical trials of Huperizine A have demonstrated positive effects on which of the following?
a. Short-term memory
b. Activities of daily living
c. Ambulation
d. Hiccup

30. The most commonly reported side effects of Huperizine A are:
a. central cholinergic.
b. peripheral cholinergic.
c. liver toxicity.
d. cardiac toxicity.
e. renal toxicity.

With Comments from John La Puma, MD, FACP

Antioxidants and Alzheimer's Disease: The Rush Study

Source: Morris MC, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer disease in a biracial community study. *JAMA* 2002;287:3230-3237.

OXIDATIVE PROCESSES HAVE BEEN suggested as elements in the development of Alzheimer's disease (AD), but whether dietary intake of vitamin E and other antioxidant nutrients prevents its development is unknown.

To examine whether intake of antioxidant nutrients, vitamin E, vitamin C, and beta-carotene, is associated with incident AD, a prospective study was conducted from 1993 to 2000, of individuals selected in a stratified random sample of community-dwelling residents in Chicago. The 815 residents ages 65 years and older were free of AD at baseline and were followed for a mean of 3.9 years. They completed food frequency questionnaires an average of 1.7 years after baseline.

The primary outcome studied included incident AD diagnosed in clinical evaluations with standardized criteria.

Increasing vitamin E intake from foods was associated with decreased risk of developing AD after adjustment for age, education, sex, race, APOE*e4, and length of follow-up. Relative risks (95% confidence intervals [CIs) from lowest to highest quintiles of intake were 1.00, 0.71 (0.24-2.07), 0.62 (0.26-1.45), 0.71 (0.27-1.88), and 0.30 (0.10-0.92) (P for trend = 0.05). The protective association of vitamin E was observed only among persons who were APOE 4 negative. Adjustment for other dietary factors reduced the protective association.

After adjustment for baseline memory score, the risk was 0.36 (95% CI 0.11-1.17). Intake of vitamin C, beta-carotene, and vitamin E from supplements was not significantly associated with risk of AD. This study suggests that vitamin E from food, but not other antioxidants, may be associated with a reduced risk of AD. Unexpectedly, this association was observed only among individuals without the APOE*e4 allele.

COMMENT

This study, by Rush University investigators, found that a vitamin E rich diet, but not vitamin E supplements, reduced the risk of AD in older adults with the apolipoprotein E*e4 (APOE*e4) allele. A previous randomized controlled trial found that very high doses of vitamin E (2,000 IU daily) did not affect the mental status examination results of patients with advanced AD, but did delay ADL loss and death.

Apolipoprotein E is encoded by the APOE*e4 gene on chromosome 19, and is one of the major lipid transport proteins in the brain. Individuals have an APOE genotype, with the presence or absence of the APOE*e4 allele. Some 34-65% of individuals with AD carry the APOE*e4 allele, but it is present in only 24-31% of the general population: just 28% in the Rotterdam study, below. With a greater number of APOE*e4 alleles, a patient's risk of AD increases and the age of AD onset decreases. Having an allele roughly triples the risk of the disease, but it is not 100%: Most people with the gene don't get AD.

This may be the clue to why family history seems to be important in AD: the presence of the genotype APOE*e4 and its alleles, and perhaps the protein it encodes. Prospective studies of food's affects on people who carry those alleles are unlikely to be conducted, but not a far-fetched concept. The new science of nutrigenomics can, it promises, target dietary advice based on your genome. It suggests that what you should eat depends on your own DNA, and not the latest and most general rule.

For example, vitamin E protected only those who were APOE*e4 negative. But this finding contradicts in part what's known about APOE*e4 and heart disease: Those with APOE*e4 alleles who are therefore at risk for heart disease can leverage their genes with a heart-healthy diet more effectively than can those people other genotypes. The same gene may code for a protein that acts differently in different diseases.

The investigators found that subjects with greater intake of vitamin E from food tended to be men and to have a higher intake of fat and beta-carotene and lower intake of vitamin C. Subjects with high food intake of vitamin C tended to be women and to have a lower intake of vitamin E and total fat. The study did not include flavonoid analysis, and subjects completed the nutrition questionnaire just two years before their AD diagnosis. So, the inability to record all foods may have been due, in some cases, to undetected early onset.

Taking food as medicine, for many Americans, is not as appealing as taking pills for what ails them. But an emerging literature suggests that there's more to food than flavor, texture, color—and reward, companionship, and comfort. There's medicine.

Recommendation

Good food sources of vitamin E include whole grains, nuts, milk, and egg yolks. As a fat-soluble vitamin, it is better absorbed in the presence of a little (dietary) fat. Recommend that patients eat these foods, though additional modest doses of vitamin E from supplements will probably do no harm. Advanced AD patients should still receive 2,000 IU daily of supplemental vitamin E. ❖

Antioxidants and Alzheimer's Disease: The Rotterdam Study

Source: Engelhart MJ et al. Dietary intake of antioxidants and risk of Alzheimer disease. *JAMA* 2002;287:3223-3229.

LABORATORY FINDINGS HAVE SUGgested that oxidative stress may

contribute to the pathogenesis of Alzheimer's disease (AD). The risk of AD might be reduced by intake of antioxidants that counteract the detrimental effects of oxidative stress.

To determine whether dietary intake of antioxidants is related to risk of AD, The Rotterdam Study, a population-based, prospective cohort study was conducted in the Netherlands. The subjects totaled 5,395 participants who, at baseline (1990-1993), were age 55 or older, free of dementia, and noninstitutionalized and had reliable dietary assessment. Participants were reexamined in 1993-1994 and 1997-1999 and were continuously monitored for incident dementia.

The primary outcome was incidence of AD, based on Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) criteria and National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA) criteria, associated with dietary intake of beta-carotene, flavonoids, vitamin C, and vitamin E.

After a mean follow-up of six years, 197 participants developed dementia, of whom 146 had AD. When adjustments were made for age, sex, baseline Mini-Mental State Examination score, alcohol intake, education, smoking habits, pack-years of smoking, body mass index, total energy intake, presence of carotid plaques, and use of antioxidative supplements, high intake of vitamin C and vitamin E was associated with lower risk of AD (rate ratio [RR] per 1-SD increase in intake were 0.82, 95% confidence interval [CI] 0.68-0.99 and 0.82, 95% CI 0.66-1.00, respectively). Among current smokers, this relationship was most pronounced (RR 0.65, 95% CI 0.37-1.14 and 0.58, 95% CI 0.30-1.12, respectively) and also was present for intake of beta-carotene (RR 0.49, 95% CI 0.27-0.92) and flavonoids (RR 0.54, 95% CI 0.31-0.96). The associations did not vary by education or apolipoprotein E genotype. High dietary intake of vitamin C and vitamin E may lower the risk of AD.

COMMENT

Oxidative processes appear to contribute to Alzheimer's disease—the free radicals the body produces exacerbate the disruption of lipid membranes and damage to DNA. The brain is especially susceptible to oxidative stress—so much cholesterol and oxygen, so few antioxidants.

The Rotterdam study, based in Erasmus University in Rotterdam, is a well-known, population-based, prospective cohort study of the frequency and determinants of neurological, cardiovascular, locomotor, and ophthalmologic diseases in elderly persons. Nearly 80% of the inhabitants of Rotterdam participated.

Like the Rush study, the Rotterdam study examined protein E (from APOE*e4) and antioxidant intake. Also like the Rush study, it found that food was the key—at baseline, flavonoid intake, but not beta-carotene, vitamin C, or vitamin E intake, was significantly associated with higher Mini-Mental Status Examination scores. A high intake of foods rich in vitamins C and E (but not vitamin supplements) was associated with reduced risk of AD. Flavonoids, beta-carotene, and supplements were not related to the risk of AD at follow-up.

Smokers, as expected, had less risk of AD with higher intake of beta-carotene and flavonoids. What was the difference reported for those with at least one APOE*e4 allele? More antioxidants (except flavonoids) were better and associated with a lower risk of AD.

The Rotterdam study differs from the Rush study—in subject age, number, demographics, tobacco use, follow-up, and of course genetics. Only one dietary recall session was used—again, an unfortunate way to assess intake accurately and comprehensively. But this study too is best-of-its-kind-so-far data.

How antioxidants—of any type—act to prevent AD is uncertain. Antioxidants may decrease the level of neural oxidative stress, and in the same way diminish neural DNA damage and cell death. Oxidative stress in brains of Alzheimer patients is indicated by elevated cerebral levels of endogenous antioxidants that scavenge free radicals. Lab and animal studies show that exogenous antioxidants reduce the toxicity of beta-amyloid protein and the immune cells which combine to make amyloid plaques in the brains of patients with AD.

Recommendation

Foods that are rich in flavonoids include cranberries, green and black tea, strawberries, apples, grapes and red wine, onions, tomatoes, and citrus fruit. Foods rich in vitamin C include kiwis, red and green bell peppers, papayas, strawberries, oranges, and mangos. Foods that are rich in vitamin A include pumpkin, sweet potato, cantaloupe, carrots, spinach, and mango—and fortified breakfast cereal, which is an excellent source. Smokers who want to try to avoid AD should get their fill. ❖

In Future Issues:

Cranberry (*Vaccinum macrocarpon*) and Urinary Tract Infection

Nuts for the Treatment of Hypercholesterolemia: Seeds of Change?

Flower Remedies for Stress Relief