AMERICAN HEALTH CONSULTANTS

ALTERNATIVE MEDICINE ALERT

The Clinician's Evidence-Based Guide to Complementary Therapies

Alternative Medicine Reports included with this issue

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

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

Eye Movement Desensitization and Reprocessing (EMDR) for Post-Traumatic Stress Disorder

By Judith L. Balk, MD, FACOG

POST-TRAUMATIC STRESS DISORDER (PTSD) IS A FAIRLY COMMON DISorder. Roughly 8-10% of the population will suffer from PTSD at some point in their lives. For victims of violent crimes such as rape, the rate of PTSD may be 60-80%.[1]

According to the DSM-IV, diagnostic criteria for PTSD include: 1) perceived or actual threat to life or physical integrity, accompanied by an emotional response of horror, helplessness, or intense fear; 2) re-experience of the trauma (e.g. flashbacks and nightmares); 3) avoidance of trauma-related stimuli and numbing of interest and affect; and 4) increased unwanted arousal, such as concentration difficulties, irritability, and insomnia. Specific criteria exist regarding the numbers of symptoms in each category that must be present.

Eye movement desensitization and reprocessing (EMDR) appears to be an effective adjunctive treatment for PTSD, but EMDR is difficult to study and may be dependent on eye movement.

Trauma Sequelae

Trauma can violate three basic premises: the belief in personal invulnerability, the perception of the world as meaningful, and the positive view of self.[1] PTSD may occur from seemingly diverse events such as rape, combat, assault, and bereavement. These events are similar in that they all disturb one's pre-existing view of the self and the world.

Treatment for PTSD

Treatment for PTSD strives to develop realistic assessments of the hazard from the trauma and the options for response that were available at the time of the trauma. Psychological approaches such as providing a safe environment in which to explore and re-experience the event are important, as is learning to conquer cue avoidance—cues that elicit memories of the trauma.

Both medication and psychological approaches have been used. The efficacy of treatments for both combat- and non-combat-related

Volume 4 • Number 11 • November 2001 • Pages 121-132

INSIDE

PTSD has been reviewed.[2,3] Psychological therapies are more effective than drug therapies, which are more effective than controls. Selective serotonin reuptake inhibitors and carbamazepine are the most effective among the drug therapies; behavior therapy and EMDR are the most effective of the psychological treatments.[3]

EMDR

EMDR is a controversial procedure that was developed by Francine Shapiro, PhD. In her initial 1989 paper, she wrote that she discovered the effect of the eye movements accidentally when she noticed that recurring, disturbing thoughts unexpectedly resolved:[4]

"Careful self-examination ascertained that the apparent reason for this effect was that the eyes were automatically moving in a multi-saccadic manner while the disturbing thought was being held in consciousness."

She noted that the thought disappeared, and if then deliberately retrieved, it was not emotionally disturbing. Dr. Shapiro began systematically using the eye movements for therapy, suggesting that the procedure had the capacity to desensitize a highly traumatic memory, produce cognitive restructuring, and cause substantial behavior changes.

EMDR Procedure

The EMDR procedure incorporates some aspects of traditional psychotherapy with the eye movements. Overall, patients are asked to follow the therapist's finger with their eyes. The therapist moves his/her finger very rapidly side to side 10-20 times as a means of eliciting rhythmic, bilateral saccadic eye movements. At the same time, the patient visualizes the traumatic event and internally repeats the associated irrational cognition or negative self-statement. This procedure may be repeated multiple times. The practice of EMDR has eight formal phases. These are explained in Table 1.

Trained physicians or psychologists perform this procedure in the office. Treatments last roughly 50 minutes each and typically are repeated several times, although studies range from one to 12 sessions.

Although the eye movements are crucial in the name of the procedure, "eye movement desensitization and reprocessing," some have questioned whether eye movements truly are necessary for the treatment to be effective. Several studies have found that keeping the eyes stationary during the procedure is as effective as standard EMDR. Others have replaced the eye movements with other forms of stimulation such as using a light-tracking apparatus or thumb tapping in time with a metronome.[5] The eye movements are considered to be one element in the "package" of therapeutic elements. These other therapeutic elements are parts of standard therapeutic approaches, such as cognitive behavioral therapy. Although Dr. Shapiro may have noticed during a walk that her back-and-forth eye movements reduced the aversiveness of her troubling thoughts,[6] no self-treatment approaches have been studied or recommended.

Mechanism of Action

One reason why EMDR is controversial is that it was not developed from a specific theoretical position; instead, it was developed from a serendipitous observation. That said, theories have evolved to explain a possible mechanism of action.

Shapiro postulates that with severe trauma, an imbalance occurs in the nervous system. The system holds, or is blocked by, the unprocessed disturbing information that is encoded neurologically. The eye movements, or any type of lateral stimulation, are proposed to facilitate information processing. With each set of eye movements, the disturbing information is thought to move at an accelerated rate further along the neuropsychological pathways, thus leading to neurobiological and psychological effects.[7]

Autonomic changes such as decreased blood pressure and heart rate have been found with EMDR compared to

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.
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: $42 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Professional counsel should be sought for specific situations. The publication is not intended for use by the layman.

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
$299 per year (Student/Resident rate: $125).
Multiple Copies
1-9 additional copies: $224 each; 10 or more copies: $199 each
Outside the United States
$329 per year plus GST (Student/Resident rate: $140 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 Prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of July 1, 2001. 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.

AMERICAN HEALTH CONSULTANTS
THOMSON HEALTHCARE

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.

Conflict of Interest 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. Alschuler, Dr. Balk, Dr. Barrette, Dr. Cirigliano, Dr. deLeon, Dr. Gaster, Dr. La Puma, Dr. Ramalanjaona, Dr. Ring, Dr. Schiedermayer, and Dr. Sorrentino have no relationships with companies related to the field of study covered by this CME program.

Table 1

Eight stages of EMDR

Stage 1	Patient history and treatment planning
Stage 2	Preparation
Stage 3	Assessment
Stage 4	Desensitization and reprocessing
Stage 5	Installation of positive cognition
Stage 6	Body scan
Stage 7	Closure
Stage 8	Re-evaluation

Adapted from: Chemtob C, et al. Eye movement desensitization and reprocessing. In: Foa E, et al, eds. *Effective Treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies.* New York: The Guilford Press; 2000:139-154.

Table 2

"Gold standard" research methodology

1. Clear definition of PTSD or symptoms that are being targeted
2. Valid and reliable measures
3. Use of blinded evaluators
4. Assessor training
5. Replicable, specific treatment programs, detailed in treatment manuals
6. Unbiased assignment to treatment (randomization)
7. Rating of treatment adherence

Adapted from: Foa EB, Meadows EA. Psychosocial treatments for posttraumatic stress disorder: A critical review. *Annu Rev Psychol* 1997;48:449-480.

control conditions that were similar but had no eye movements.[8] In addition, a single photon emission computed tomography (SPECT) study suggests that EMDR and successful treatment of PTSD do not reduce arousal at the limbic level, but instead enhance the ability to differentiate real from imagined threat.[9]

Clinical Trials

Performing randomized, controlled, blinded trials with EMDR is challenging. Methodological issues concern the varying presentation of the disease, the suitability of a control group, control treatment, outcome variables, and blinding.

Although PTSD has strict criteria for diagnosis, the most troubling symptoms vary between patients, a homogenous group of subjects to study is difficult to find, and the choice of a control group also is wide. One can compare EMDR to another psychological approach (and many exist), a medication, a waiting list or no-treatment control, or to a variant form of EMDR such as using no eye movements but having all of the other components. The chosen outcome variables must be valid, reliable, and indicative of all the major symptoms of PTSD. Comorbidity, such as depression and panic disorder, also must be taken into account. Finally, it is impossible to blind for either subject or researcher. Thus, ideally, the investigator performing the assessments will be blinded to treatment group. "Gold standards" for treatment outcomes studies of PTSD are listed in Table 2.[10]

The first controlled trial was published by Dr. Shapiro.[4] In this study, 21 volunteers suffering from "traumatic memories" were randomized to receive either treatment with EMDR or a placebo treatment. Those who were assigned to placebo treatment received EMDR after the placebo treatment; this group became the delayed treatment group. A single session of EMDR successfully desensitized the subjects' traumatic memories and altered their cognitive assessments of the trauma. These effects were maintained through the three-month follow-up period. The study lacked most of the gold standards noted in Table 2, including eligibility criteria, standardized measures, and blind evaluations.

A more rigorous study randomized 36 subjects with PTSD to wait list or non-wait list EMDR, image habituation training, or applied muscle relaxation.[11] Assessor and self-reports evaluated outcome variables. All three treatment groups improved significantly compared to a wait list control. The authors concluded that EMDR is as helpful as the other approaches studied.

Other rigorous studies have compared standard EMDR to EMDR without eye movement. Seventeen Vietnam veterans with PTSD enrolled in a crossover study using the two treatment approaches.[12] Both groups had modest to moderate overall improvement. The authors concluded that factors other than eye movements are responsible for EMDR's therapeutic effect.

Other reviews and meta-analyses have been published on EMDR as a treatment for PTSD.[6,13,14] One review argues that "EMDR provides an excellent vehicle for illustrating the differences between scientific and pseudoscientific therapeutic techniques."[14] A different review concludes, "In sum, EMDR appears to be no more effective than other exposure techniques, and evidence suggests that the eye movements integral to the treatment, and to its name, are unnecessary."[13] Another review concludes that "EMDR is an effective psychotherapy...EMDR's relative efficacy in comparison to behavioral exposure therapies has yet to be established."[7] Clearly, the evidence is conflicting. Heterogeneity in the research studies limits the conclusions that can be drawn.

Conclusion

Although a comparative conclusion is not yet possible, EMDR appears to be an effective adjunctive treatment for PTSD. Whether eye movements are necessary is unclear, as the role of the eye movements is unknown. Keeping the eyes stationary and other forms of stimulation may be effective. If eye movements are unnecessary, EMDR becomes another psychotherapeutic technique that may include helpful components of other psychotherapeutic techniques in one treatment package.

Recommendation

Patients suffering from PTSD should be encouraged to seek psychological therapy, which may include EMDR methodologies. ❖

References

1. Solomon S. Psychosocial treatment of posttraumatic stress disorder. *In Session: Psychotherapy in Practice* 1997;3/4:27-41.
2. Solomon SD, et al. Efficacy of treatments for posttraumatic stress disorder. An empiric review. *JAMA* 1992; 268:633-638.
3. VanEtten ML, Taylor S. Comparative efficacy of treatments for post-traumatic stress disorder: A meta-analysis. *Clin Psychol Psychother* 1998;5:126-144.
4. Shapiro F. Efficacy of the eye movement desensitization procedure in the treatment of traumatic memories. *J Traumatic Stress* 1989;2:199-223.
5. Cahill SP, et al. Does EMDR work? And if so, why?: A critical review of controlled outcome and dismantling research. *J Anxiety Disord* 1999;13:5-33.
6. Chemtob C, et al. Eye movement desensitization and reprocessing. In: Foa E, et al, eds. *Effective Treatments for PTSD: Practice Guidelines from the International Society for Traumatic Stress Studies*. New York: The Guilford Press; 2000:139-154.
7. Spector J, Read J. The current status of eye movement desensitization and reprocessing (EMDR). *Clin Psychol Psychother* 1999;6:165-174.
8. Wilson DL, et al. Eye movement desensitization and reprocessing: Effectiveness and autonomic correlates. *J Behav Ther Exp Psychiatry* 1996;27:219-229.
9. Levin P, et al. What psychological testing and neuroimaging tell us about the treatment of Posttraumatic Stress Disorder by Eye Movement Desensitization and Reprocessing. *J Anxiety Disord* 1999;13:159-172.
10. Foa EB, Meadows EA. Psychosocial treatments for posttraumatic stress disorder: A critical review. *Annu Rev Psychol* 1997;48:449-480.
11. Vaughan K, et al. A trial of eye movement desensitization compared to image habituation training and applied muscle relaxation in post-traumatic stress disorder. *J Behav Ther Exp Psychiatry* 1994;25:283-291.
12. Pitman RK, et al. Emotional processing during eye movement desensitization and reprocessing therapy of Vietnam veterans with chronic posttraumatic stress disorder. *Compr Psychiatry* 1996;37:419-429.
13. Davidson PR, Parker KC. Eye movement desensitization and reprocessing (EMDR): A meta-analysis. *J Consult Clin Psychol* 2001;69:305-316.
14. Herbert JD, et al. Science and pseudoscience in the development of eye movement desensitization and reprocessing: Implications for clinical psychology. *Clin Psychol Rev* 2000;20:945-971.

Effects of Phosphatidylserine on Alzheimer's Disease and Age-Related Memory Loss

By Georges Ramalanjaona, MD, DSc, FACEP, MBA

AS A DIETARY SUPPLEMENT, PHOSPHATIDYLSERINE (PS) has been used widely in Europe for more than 15 years to treat various forms of dementia and depressive disorders, as well as normal age-related memory impairment. Although relatively unknown in the United States, PS is commercially available and is the best-validated supplement studied (16 controlled and 11 double-blind studies) for age-related memory loss and shows potential benefits in slowing the rate of deterioration of early Alzheimer's disease.[1,2] Furthermore, preliminary research indicates that PS is useful for the treatment of depression in the elderly.[3]

This report will examine the best, current evidence on the role of PS in the treatment of Alzheimer's disease, depressive states, and age-related memory loss.

Pharmacokinetics

PS is a complex, fat-soluble phospholipid molecule manufactured by the body in a series of steps. It is found only in trace amounts in a typical diet, but in large quantity in green leafy vegetables, fish, and soy. Following oral intake, this substance is absorbed through the gastrointestinal tract and crosses the blood-brain barrier, where it is found in high concentration and is involved in neuronal cell membrane structure and function.[4]

Experimental animal studies show that PS induces brain biochemical and morphological changes by acting on the neurotransmitter system through its effects on membrane properties and the receptor-synaptic system.[5,6]

Table

Recent studies on the effects of PS on neuropsychiatric disorders

Study	Design	Subjects	Dosage	Duration	Results
Maggioni M, et al[3]	Crossover, placebo-controlled	10 geriatric women	300 mg/d PO	45 days	Consistent improvement of depressive symptoms, memory, and behavior.
Crook T, et al[16]	Randomized, double-blind, placebo-controlled	149 adults	100 mg PO tid	12 weeks	Improvement on neuro-psychological and performance tests vs. placebo.
Cenacchi T, et al[15]	Randomized, double-blind, placebo-controlled, multicenter	494 geriatric patients	100 mg PO tid	24 weeks	Statistically significant improvement in PS-treated group on behavior and cognitive tests vs. placebo.
Engel RR, et al[2]	Crossover, double-blind, placebo-controlled	33 adults	300 mg/d PO	8 weeks	Lasting and mild improvement in brain function behavior in PS-treated dementia patients vs. placebo.
Crook T, et al[1]	Randomized, double-blind, placebo-controlled	51 geriatric patients	300 mg/d PO	12 weeks	Significant improvement of cognitive test in PS-treated Alzheimer's patients vs. placebo.

Limited human studies confirm that radioactive-labeled PS concentrates highly in the brain, and positron emission tomography scans demonstrate increased glucose utilization and oxygen uptake in the brain, indicative of high metabolism activity following PS ingestion.[7,8]

Mechanism of Action

Bovine cortex phosphatidylserine (BC-PS), a pharmacologically active form of PS, enhances catecholaminergic neurotransmission and acetylcholine release and synthesis in brains of aged rats.[9] It also prevents age-induced loss of dendritic spines in hippocampal pyramidal neurons and atrophy of cholinergic cells in the basal forebrain of aged rodents.[6] As a result, administration of BC-PS improves learning and memory functions in these animals. Also, recent animal studies show BC-PS reverses chemical-induced amnesia.[10]

In vitro, BC-PS decreases cell death induced by xanthine oxidase.[11]

In healthy human volunteers, BC-PS neutralizes the adrenocortical activation induced by physical stress. This leads to the release of cortisol, which induces the formation of plaque in brain associated with Alzheimer's disease (AD).[12] It also stimulates release of acetylcholine and produced more relaxing alpha waves as quantitatively assessed by electroencephalogram.[7]

Clinical Studies

Overall, the scientific evidence for effectiveness of PS in dementia is very strong (Grade I in evidence-based grading of evidence) and strong (Grade II) for age-associated memory loss.

Eleven randomized, double-blind, placebo-controlled trials involving more than 1,000 patients show that BC-PS is an effective and safe treatment for early AD and other forms of dementia.[1,2,13] Results show that patients with AD treated for 8-12 weeks with 300 mg/d of BC-PS display significant improvement on several cognitive measures (memory assessment clinics) vs. placebo. The differences between treatment groups were apparent among patients with less severe cognitive impairment, suggesting that PS may be useful in early stages of AD.

The largest of these studies followed 494 geriatric patients over a six-month period. All of the patients displayed moderate to severe cognitive decline as measured by standardized tests. The results show statistically significant improvements in the PS-treated group ($P < 0.05$) compared to placebo both in terms of behavioral and cognitive parameters.[1] This finding is clinically significant because these patients are representative of the typical geriatric population seen in clinical practice. These results are in agreement with smaller randomized, double-blind, placebo-controlled trials of more than 500 patients with Alzheimer's or other age-related dementia

followed over a short period of time.[2,14] These studies consistently show lasting and statistically significant improvement in cognitive tests and brain function behavior in PS-treated dementia and Alzheimer's patients vs. placebo.

Current literature with good evidence (Grade II) shows that PS improves ordinary age-associated memory loss commonly seen in individuals age 50 and older. Results of a multicenter, fully randomized, double-blind, placebo-controlled trial indicate improvement equivalent to 12 years of de-aging in the PS-treated group taking 300 mg/d of PS for 12 weeks compared to the placebo group on both neuropsychological performance (learning, memory) and clinical global ratings (cognitive, behavioral domains).[15,16] Patients with the most severe memory loss showed the most improvement on the parameters. The efficiency of PS compared to placebo was measured on the behavioral and cognitive performance tests of the Plutchik Geriatric Rating Scale and the Buschke Selective Reminding Test at three and six months after therapy.

In addition, further clinical evaluations and laboratory tests showed that BC-PS is well tolerated. These results are clinically important because these patients are representative of the geriatric population commonly seen in clinical practice (i.e., patients with multiple pathologies and on multiple drugs). In this setting, administration of BC-PS together with other drugs failed to show any pharmacological interactions as judged by clinical signs and symptoms for 3-6 months.[15]

At the time of this publication, there are no known ongoing human clinical trials at the National Institute of Mental Health studying the effects of PS on mental disorders or meta-analyses summarizing the existing effects of PS.

Adverse Effects

In short-term trials, no adverse events attributable to PS have been noted. In long-term clinical trials, side effects are rare and clinically unimportant, and have been limited to mild gastrointestinal symptoms.[15]

There is the potential concern that PS may interact with the anticoagulant heparin. This is clinically important for those patients taking heparin for short- or long-term treatment, such as in the prevention or treatment of pulmonary embolus or deep venous thrombosis.

There are no other reported contraindications or precautions with the use of PS for AD and depression.

Regulation

PS is readily and commercially available as a dietary supplement in the United States, and because it is a natural substance, it is not regulated as a drug by the U.S. Food and Drug Administration.

Formulation

In the United States, most research has been conducted with PS derived from cow brain tissue. However, due to the concerns about possible infectious disease transmission, soy-based PS supplements are beginning to replace bovine-based PS. Although sales of bovine-based PS have declined because of fear of contracting Mad Cow disease, no such incident has been reported in the United States.

Soy- and bovine-derived PS are not structurally identical (bovine-derived PS contains the omega-3 fatty acid DHA, which is not found in the soy form) and only a few clinical trials have studied the effects of soy-based PS.[17] Nevertheless, recent animal studies comparing PS from different sources (egg, soy, and cow brain) have found that injectable soy PS is similar to cow PS in terms of mechanism of action.[9]

Dosage

The standard dosage of PS in virtually all the published clinical trials is 100 mg three times a day. Only a few studies have used 200 mg twice a day. After achieving the full therapeutic effects, a lower dosage of 100 mg once daily may be sufficient to maintain good results in long-term studies.

High doses of cow and soy PS (800 mg/d) have been shown to modify the hormonal stress responses to exercise in healthy humans.[18] Maximum safe doses in nursing or pregnant woman, children, and adults with severe kidney or liver diseases have not yet been established.

Conclusion

A large body of clinical data from many well-designed clinical trials has demonstrated the effectiveness of PS for the treatment of age-associated memory loss and cognitive decline in early Alzheimer's disease and depressive disorders *(see Table)*.

Based on short-term and long-term data, PS doses of 300 mg/d appear to be safe and have been associated with infrequent and minor side effects.

Recommendation

PS constitutes an addition to the natural armamentarium available to assist in the symptomatic improvement of patients with senility and dementia.

Based on available data, PS in a total daily dose of 300 mg could be used as a safe and effective alternative to other drugs for treatment of age-related memory loss and cognitive decline of early Alzheimer's disease. Further clinical trials are needed to compare the relative

effectiveness of PS to accepted therapy for the above diseases.

At this time, based on available data, PS cannot be recommended to treat or halt the progression of late-stage Alzheimer's disease or dementia. ❖

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. Crook T, et al. Effects of phosphatidylserine in Alzheimer's disease. *Psychopharmacol Bull* 1992;28: 61-66.
2. Engel RR, et al. Double-blind cross-over study of phosphatidylserine vs. placebo in patients with early dementia of the Alzheimer's type. *Eur Neuropsychopharmacol* 1992;2:149-155.
3. Maggioni M, et al. Effects of phosphatidylserine therapy in geriatric patients with depressive disorders. *Acta Psychiatr Scand* 1990;81:265-270.
4. Svennerholm L, et al. Membrane lipids in the aging human brain. *J Neurochem* 1991;561:2051-2059.
5. Furushiro M, et al. Effects of oral administration of soybean lecithin transphosphatidylated phosphatidylserine on impaired learning of passive avoidance in mice. *Jpn J Pharmacol* 1997;75:447-450.
6. Sakai M, et al. Pharmacological effects of phosphatidylserine enzymatically synthesized from soybean lecithin on brain functions in rodents. *J Nutr Sci Vitaminol* 1996;42:47-54.
7. Heiss WD, et al. Long-term effects of phosphatidylserine, pyritinol and cognitive training in Alzheimer's disease. A neuropsychological, EEG, and PET investigation. *Dementia* 1994;5:88-98.
8. Klinkhammer P, et al. Effect of phosphatidylserine on cerebral glucose metabolism in Alzheimer's Disease. *Dementia* 1990;1:197-201.
9. Blokland A, et al. Cognition-enhanced properties of subchronic phosphatidylserine (PS) treatment in middle-aged rats: Comparison of bovine cortex PS with egg PS with soybean PS. *Nutrition* 1999;15:778-783.
10. Alves CS, et al. Phosphatidylserine reverses reserpine-induced amnesia. *Eur J Pharmacol* 2000;404:161-167.
11. Sun AY, Sun GY. Neurochemical aspects of the membrane hypothesis of aging. *Interdispl Topics Gerontol* 1979;15:34-53.
12. Monteleone P, et al. Blunting by chronic phosphatidylserine administration of the stress-induced activation of the hypothalamo-pituitary-adrenal axis in healthy men. *Eur J Clin Pharm* 1992;42:385-388.
13. Amaducci L. Use of phosphatidylserine in Alzheimer's disease. *Ann N Y Acad Sci* 1991;640:245-249.
14. Crook TH, et al. Evaluation of drugs in Alzheimer's disease and age-associated memory impairment. In: Benkert O, et al, eds. *Methodology of the Evaluation of Psychotropic Drugs*. Berlin, Heidelberg: Springer-Verlag; 1990:37-55.
15. Cenacchi T, et al. Cognitive decline in the elderly: A double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration. *Aging* (Milano) 1993;5:123-133.
16. Crook TH, et al. Effects of phosphatidylserine in age-associated memory impairment. *Neurology* 1991;41: 644-649.
17. Pepev G, et al. A review of phosphatidylserine pharmacological and clinical effects. Is phosphatidylserine a drug for the aging brain? *Pharmacol Res* 1996;33: 73-80.
18. Monteleone P, et al. Effects of phosphatidylserine on the neuroendocrine response to physical stress in humans. *Neuroendocrinology* 1990;52:243-248.

Cosmeceuticals with Vitamins A and C for Aging Skin

By Marjorie D. Alschuler, PhD, and Melinda Ring, MD

In the United States, more money is spent on skin and hair products than on education. With the aging of the baby boomer generation, the number of cosmetics consumers is growing. Baby boomers are obsessed with youth, are health conscious, and believe that they will live longer than their parents. Catering to this quest for eternal youth, the cosmetic industry has adopted many ingredients that dermatologists have proven to be clinically effective in preventing and reversing the effects of aging on the skin. Two of these ingredients commonly found in cosmeceuticals are vitamins A and C.[1]

The term "cosmeceuticals" was coined about 20 years ago by Albert M. Kligman, MD, PhD, at the annual meeting of the Society of Cosmetic Chemists. Although the term has never been legally defined, it is widely used by dermatologists and the cosmetic industry

Table

Vitamins and skin care

Vitamin	Dietary Sources	Skin Condition	Results
Vitamin A	Butter, egg yolk, fish oil, liver, green and yellow vegetables	Acne	Reduces frequency of outbreaks when applied topically or taken orally.
		Psoriasis	Condition may worsen during therapy initiation. May be used alone topically or orally, or combined with psoralens UV-A therapy to achieve results in patients whose conditions are unresponsive to either therapy alone.
		Skin cancer	May prevent formation of new lesions when taken orally.
		Sun damage	When applied topically, vitamin A helps skin repair itself faster; improves fine and coarse wrinkling; lightens brown spots; and reduces the number and size of actinic keratoses.
		Wound healing	Prevents or restores impaired wound healing caused by mediations when taken orally. Promotes an early inflammatory response.
Vitamin C	Vegetables, citrus fruits	Skin cancer	Increases in dietary vitamin C have been shown to reduce UV-induced tumors.
		Sun damage	When applied topically, reduces fine lines and wrinkles, may lessen the severity of sunburns, and helps skin regenerate.
		Wound healing	Acts as a cofactor for lysyl and prolyl hydroxylase, which stabilize collagen.

Adapted from: American Academy of Dermatology. Vitamins play an important role in the prevention and treatment of skin conditions. Available at: http://www.aad.org/PressReleases/vitamins_prevention.html. Accessed October 4, 2001.

to indicate those topical agents lying somewhere between pure cosmetics (e.g., lipstick and rouge) and pure drugs (e.g., antibiotics and corticosteroids). A cosmeceutical is a cosmetic product whose active ingredient is meant to have a beneficial physiological effect resulting from an enhanced pharmacologic action when compared to an inert cosmetic.[1,2]

Background

The two components of the aging process are intrinsic chronological aging, which is largely genetic, and extrinsic aging, which is caused by environmental influences, such as ultraviolet (UV) light, smoking, wind, nutrition, and chemical exposure.

Chronic UV light exposure contributes most significantly to extrinsic aging and causes coarseness, lentigines, fine lines, telangiectasias, and solar keratoses. In addition, poor arterial flow to the skin, usually the result of atherosclerosis, promotes these same lesions.

Vitamins A and C, together with vitamin E, are known as the antioxidant vitamins. Each works independently and in conjunction with other vitamins and may reduce free radical damage to DNA, which causes unwanted changes in the basic building blocks of cells and results in diseases from cancers to colds.

Vitamin A and its preventive role in night blindness were discovered in 1913. Vitamin A is one of a family of natural and synthetic derivatives collectively known as retinoids. It is a fat-soluble vitamin that occurs naturally in two forms: retinol and dehydroretinol.[3,4]

Vitamin C, also known as ascorbic acid, gained fame for its ability to cure scurvy, a vitamin deficiency disease particularly common among seamen who spent long periods of time away from fresh vegetables and citrus

fruits. Because vitamin C is a water-soluble vitamin that the human body cannot synthesize, it should be obtained daily from food or supplements.[3,4]

Mechanism of Action

Retinoids have many important biological effects such as regulating growth and differentiation in epithelial cells, diminishing malignant cell growth, and strengthening the immune system. A cytosolic receptor for retinoic acid, cellular retinoic acid-binding protein has been demonstrated in the epidermis and in dermal fibroblasts. Retinoic acid receptors, nuclear receptors specific for retinoic acid, bind to retinoids and exert their effects through differential gene modulation.[5]

Most of the research conducted on the effectiveness of retinoids has been in the treatment of acne. Prescription retinoids prevent the development of comedones, halting their progression to inflammatory lesions. Both oral and topical retinoids have been studied, though topical prescription retinoids are the mainstay for treating most of the common varieties of acne vulgaris.

Vitamin C, on the other hand, comprises equal amounts of the isomers L-ascorbic acid and D-ascorbic acid; however, only L-ascorbic acid can be absorbed percutaneously. Claims have been made that topical forms of vitamin C may reduce signs of aging, presumably by scavenging free radicals, which enhance skin carcinogenesis and photoaging and whose production is increased during exposure to UV light. In addition, vitamin C can affect the quantitative production of collagen, which normally is decreased in older skin.[6]

Vitamin C also is critical in wound healing and acts as a cofactor for several enzymes, including lysyl and prolyl hydroxylase, which stabilize collagen. Vitamin C levels commonly are low in older patients, which may contribute to slower and more difficult wound healing.[7]

Clinical Studies

Recently, controlled studies have shown that retinoids can reduce and prevent wrinkles, brown spots, and actinic keratoses. Kligman et al first noted the ability of tretinoin (trans-retinoic acid) to improve photoaged skin in mice.[8] Human and in vivo studies confirmed that retinoic acid enhances the reparative processes in photodamaged skin.[9]

The first double-blind, vehicle-controlled trial of topical tretinoin in human photoaging was performed by Weiss et al in 1988.[5] In a four-month study, 30 patients applied tretinoin 0.1% cream to one forearm and vehicle cream to the other. Clinical improvement was seen only in the tretinoin-treated skin ($P < 0.0001$). More than 90% of the patients presented with a retinoid dermatitis, which did not prevent them from completing the study. These studies have shown that topical tretinoin improves fine and coarse wrinkling, diminishes tactile roughness, lightens solar lentigines, and reduces the number and size of actinic keratoses. Patients reported noticeable improvement in skin texture and tone after starting a retinoic acid treatment program; those with more severely damaged skin showed the most improvement.

In 1997, Duell et al found topical retinol had increased skin penetration compared to retinoic acid, without the irritation caused by retinoic acid.[10] These investigators concluded that retinol may become a clinically useful product due to its low irritation potential and potent retinoid activity.

Murray et al treated the volar forearms of 10 volunteers with a 10% L-ascorbic acid solution or vehicle control.[11] After UVB irradiation, sites treated with topical vitamin C showed a significant reduction of the minimal erythema dose and a less intense erythematous response than controls. In other studies, human sunburn cells decreased and improvement occurred after three days of UV-B exposure to sites treated with 10% topical vitamin C 15-30 minutes prior to exposure.[7]

Adverse Effects

Although a minimum of 24 weeks of tretinoin therapy usually is needed to manifest visible signs of improvement, many patients discontinue therapy, thus reversing any positive results, because of untoward side effects, including irritation, dryness, and redness. A retinoid skin reaction consisting of xerosis and mild inflammation has been the only use-limiting side effect reported in photodamaged skin treated with topical tretinoid, and patients will tolerate the reaction best if they are informed in advance of its likely occurrence.[5] Topical retinol use, on the other hand, produces less irritation.[7] Topically, vitamin C is safe in high levels for prolonged periods due, in part, to its water solubility.

Regulations

Retinoic acid currently is the only medication approved by the U.S. Food and Drug Administration as safe and effective for reversing some of the effects of skin damage and is available only by prescription. Retinol, the parent compound, is metabolized in the body to retinoic acid and has "grandfather" status under the Dietary Supplement Health and Education Act of 1994, which allows retinol to be marketed without proof of safety and efficacy.

In addition, the cosmetic industry is not held to the same regulatory standards as the pharmaceutical industry. Drugs must establish minimum good manufacturing

practices for each batch of finished product in regard to their active ingredient; cosmetics are not required to list the ingredients in each product. Although the cosmetic products do indeed contain vitamins A and C, they may not be formulated in the optimal doses, administered via the optimal route, or offer the chemical activity level proven effective in the controlled trials.

The U.S. cosmetic industry is regulated by the Federal Trade Commission and cannot engage in unfair or deceptive acts or practices regarding the promotion of its products.

Merchandising

Recent articles dispute the subjective claims of the cosmetic industry, which are difficult to measure clinically.[1,2] Some contend that vitamin-containing products are natural appeals to consumers who are suspicious of anything synthetic and assume that a substance that is found naturally in the body will provide benefits when administered in large doses, either oral or topical. Furthermore, many well-formulated skin care products, regardless of their ingredients, may improve the appearance of photodamaged skin simply due to their basic formulations (i.e., good moisturizers enjoy the long-recognized benefits of emollients in moderating common skin conditions).[1,2]

To counter these criticisms, one company funded an independent research center whose purpose is to perform scientific investigations into the biology and physiology of healthy skin and to establish synergistic connections between dermatology and cosmetic research.[12] Another joined with Harvard University and Massachusetts General Hospital (MGH) to establish the MGH/Harvard Cutaneous Biology Research Center.[13]

Although they do not cite specific studies, many cosmetic companies do make claims about the efficacy of their products in their brochures, advertisements, and web sites. Consumers can purchase both top-end ($50 and up) and lower-end ($16 for Avon Anew Line Eliminator Dual Retinol Facial Treatment) cosmetic products containing antioxidants and retinol to treat fine lines, wrinkles, dark spots, and uneven texture. Daytime products also contain sunblock SPF 15 or higher. Because retinol degrades in sunlight, products containing this ingredient are recommended for overnight application.

Conclusion

Retinoic acid, a derivative of vitamin A, has been shown to reduce and prevent wrinkles, brown spots, and actinic keratoses in controlled studies. Beginning with Weiss's 1988 vehicle-controlled trial of topical tretinoin, clinicians have found significant improvement in patients' skin texture and tone. However, a retinoid dermatitis, consisting of xerosis and mild inflammation, did occur in most patients. Recent studies have found that topical retinol has greater skin penetration than topical retinoic acid with potent retinoid activity and lower irritation potential. Topical vitamin C was shown by Murray et al to significantly reduce the erythmatous response to UV radiation, demonstrating its potential as a photodamage preventive.

Recommendation

Prevention is the best strategy for retaining healthy youthful skin. Avoid exposure to direct sunlight, use sunscreen with SPF of at least 15 year-round, and wear protective clothing. Advanced signs of aging may require prescription medications under the supervision of a dermatologist. Cosmetics containing vitamins A or C can provide some relief from the signs of aging while preventing further damage, and there appear to be no harmful side effects. ❖

Dr. Alschuler is Medical Education Specialist and Dr. Ring is Clinical Training Attending Physician and Coordinator, CAM Curriculum, Internal Medicine Residency Training Program, St. Joseph Hospital, Chicago, IL.

References

1. Kligman AM. Cosmetics. A dermatologist looks to the future: Promises and problems. *Dermatol Clin* 2000; 18:699-709.
2. Kligman D. Cosmeceuticals. *Dermatol Clin* 2000;18: 609-615.
3. The antioxidant vitamins A and C. *Altern Med Alert* 2000;3(Suppl 12):S1-S2.
4. Draelos ZD. Adding vitamins to the mix: Skin care products that can benefit the skin. Presentation at the American Academy of Dermatology 2000 Annual Meeting. San Francisco, CA: March 11, 2000. Available at: www.aad.org.
5. Weiss JS, et al. Tretinoin treatment of photodamaged skin. Cosmesis through medical therapy. *Dermatol Clin* 1991;9:123-129.
6. Gendler EC. Topical treatment of the aging face. *Dermatol Clin* 1997;15:561-567.
7. Keller KL, Fenske NA. Uses of vitamins A, C, and E and related compounds in dermatology: A review. *J Am Acad Dermatol* 1998;39:611-625.
8. Kligman LH, et al. The contributions of UVA and UVB to connective tissue damage in hairless mice. *J Invest Dermatol* 1985;84:272-276.
9. Kligman AM, et al. Topical tretinoin for photoaged skin. *J Am Acad Dermatol* 1986;15:836-859.

10. Duell EA, et al. Unoccluded retinol penetrates human skin in vivo more effectively than unoccluded retinyl palmitate or retinoic acid. *J Invest Dermatol* 1997; 109:301-305.
11. Murray J, et al. Topical vitamin C treatment reduces ultraviolet B radiation-induced erythema in human skin [abstract]. *J Invest Dermatol* 1991;96:587.
12. Chanel Research Centre for the Study of Healthy Skin (CERIES). More information is available at: www.chanel.com/fb/html/en/newframeset.cfm?zone=USA&lang=EN. Accessed October 3, 2001.
13. Shiseido Annual Report 2000. Available at: www.shiseido.co.jp/e/e0009anu/html/indexp.htm. Accessed October 3, 2001.

CME Questions

25. The percentage of people that will suffer from PTSD at some point in their lives is:
a. 2-4%.
b. 8-10%.
c. 20-25%.
d. 40-45%.

26. EMDR clearly is superior to other methods of treating PTSD.
a. True
b. False

27. The standard dose of PS used to treat normal age-related memory loss in virtually all of the published clinical trials is:
a. 100 mg/d.
b. 200 mg/d.
c. 300 mg/d.
d. 600 mg/d.

28. The most common side effect of PS in major clinical trials is:
a. clinical.
b. neurological.
c. gastrointestinal.
d. pulmonary.

29. Which of the following factors is the major cause of intrinsic aging of the skin?
a. Chemical exposure
b. Genetics
c. Pregnancy
d. Ultraviolet light

30. Vitamin C has been found to have little or no effect on:
a. acne.
b. fine lines and wrinkles.
c. UVB-induced erythema.
d. wound healing.

Clinical Briefs

With Comments from John La Puma, MD, FACP

Behavioral and Pharmacological Treatment of Tension Headache

Source: Holroyd KA, et al. Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: A randomized controlled trial. *JAMA* 2001;285: 2208-2215.

CHRONIC TENSION-TYPE HEADACHES are characterized by near-daily headaches and often are difficult to manage in primary practice. Behavioral and pharmacological therapies appear modestly effective, but data are lacking on their separate and combined effects.

To evaluate the clinical efficacy of behavioral and pharmacological therapies, singly and combined, for chronic tension-type headaches, Holroyd et al conducted a randomized, placebo-controlled trial from August 1995 to January 1998 at two outpatient sites in Ohio.

Two hundred three adults (mean age, 37 years; 76% women) with a diagnosis of chronic tension-type headaches (mean, 26 headache days/mo) were randomly assigned to receive tricyclic antidepressant medication (AM, amitriptyline hydrochloride, up to 100 mg/d, or nortriptyline hydrochloride, up to 75 mg/d) (n = 53); placebo (n = 48); stress management therapy (SMT, e.g., relaxation, cognitive coping; three sessions and two telephone contacts) plus placebo (n = 49); or SMT plus AM (n = 53).

Monthly index scores were calculated as the mean of pain ratings (0-10 scale) recorded by participants in a daily diary four times per day; number of days per month with at least moderate pain (pain rating 5), analgesic medication use, and Headache Disability Inventory scores, compared by intervention group.

Tricyclic AM and SMT each produced larger reductions in headache activity, analgesic medication use, and headache-related disability than placebo, but AM yielded more rapid improvements in headache activity.

Combined therapy was more likely to produce clinically significant (50%) reductions in headache index scores (64% of participants) than antidepressant medication (38% of participants; P = 0.006), stress management therapy (35%; P = 0.003), or placebo (29%; P = 0.001). On other measures, the combined therapy and its two component therapies produced similar outcomes.

The authors conclude that AM and SMT are modestly effective in treating chronic tension-type headaches. Combined therapy may result in improved outcome relative to monotherapy.

COMMENT

This is the first published placebo-controlled trial to examine the separate

and combined effects of behavioral and drug therapies for a chronic headache disorder. It is useful because it briefly describes SMT, and makes it potentially accessible to practitioners. There are methodological flaws, including a substantial number of exclusions, which make the results difficult to generalize to patients with chronic headache who have a comorbid disorder, such as a pain syndrome, or concomitant headache disorder:

"There were 206 excluded participants: Fifty-four chose not to be evaluated for the study or did not complete the pretreatment evaluation; 53 did not receive a primary diagnosis of chronic tension-type headache or received a diagnosis of analgesic-abuse headaches at the baseline evaluation; 26 experienced migraines more than one day a month; 19 were using AM, other prophylactic headache medication, or anxiolytics regularly (15 days/mo); 31 presented with a medical or psychiatric disorder that required referral; 10 were currently receiving psychotherapy; six were pregnant or planned a pregnancy; six had a pain disorder other than headache as their primary pain problem; and one had a medical contraindication to amitriptyline."

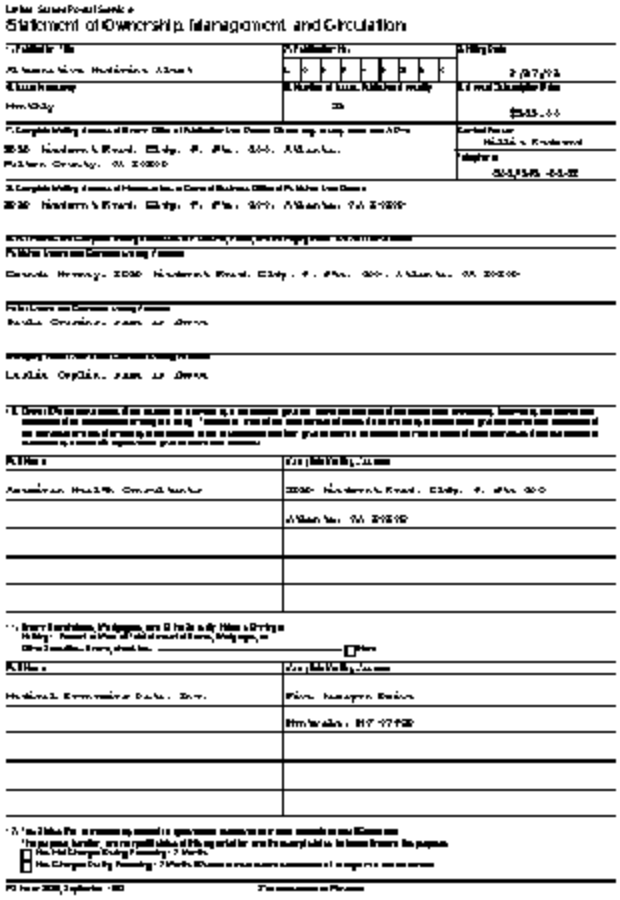
The investigators used a psychologist or counselor to administer SMT in three one-hour sessions, all at the same time as visits for medication dose adjustments. Instruction manuals and audiotapes were given, and deep muscle relaxation training of 16 muscle groups was introduced. Active cognitive coping or problem solving techniques were introduced. These skills were applied to pain management, and a review of progress to date was held.

Meds helped more quickly than SMT, but at six months both methods were significantly better than placebo. Eighty percent of the participants who received meds and 30% of participants who received placebo reported adverse effects (P = 0.001). Of nine reported adverse effects caused by AM (dry mouth, drowsiness, weight gain, dizziness, sweating, constipation, abdominal pains, nervousness, increased appetite), only dry mouth and drowsiness were reported by more than 10% of participants in either treatment group; 51 participants (53%) in the AM group reported dry mouth vs. 12 (13%) in the placebo group (P = 0.001) and 43 participants (44%) in the AM group reported drowsiness vs. 10 (11%) in the placebo group (P = 0.001).

Adverse effects from SMT were not reported.

Recommendation

The treatment of chronic tension headache is difficult and taxing, and often frustrating. Patient involvement, with identification of triggers and home-learning of problem solving and coping skills, puts the responsibility for treatment where it needs to be—helping the patient help herself. Recommend stress management therapy along with pharmacological therapy. ❖


Statement of Ownership, Management, and Circulation