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DEPRESSION

ABSTRACT & COMMENTARY

Non-seasonal Major Depressive Disorder: Bright Light Therapy and/or Fluoxetine

By Ellen Feldman, MD

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Dr. Feldman reports no financial relationships relevant to this field of study.

SOURCE: Lam RW, et al. Efficacy of bright light treatment, fluoxetine, and the combination in patients with nonseasonal major depressive disorder. *JAMA Psychiatry* 2016;73:56-63. doi:10.1001/jamapsychiatry.2015.2235.

SYNOPSIS: In this four-pronged study comparing the effect of bright light treatment, fluoxetine, a combination of these two interventions, and placebo in patients with major depressive disorder, the combination treatment appears the most consistently effective.

Judicious exposure to full-spectrum light is an accepted and effective treatment for seasonal affective disorder.[1] There has been some thought that light could potentially benefit patients with major depressive disorder (MDD) as well, given the disruption in circadian rhythm associated with depression and the effect of light exposure in restoring normal rhythms. However, until now studies have yielded conflicting evidence for this hypothesis.[2] The primary objective of this multicenter Canadian investigation was to test a dual hypothesis in adult patients with non-seasonal MDD:

1. Light treatment is more effective than placebo.
2. In combination, light treatment and antidepressant medication is more effective than either treatment alone or placebo.

One of the major downfalls of previous studies looking at light treatment in non-seasonal depression has been the lack of a sham condition (light placebo) and the relatively short length of the studies (too short to allow evaluation of response to medication.) This study attempted to address both of these issues by creating a sham-placebo arm using a negative ion generator

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Summary Points

- In this study, 122 adult patients were randomized to one of the following treatments: 1) light therapy at 10,000 lux, 30 minutes daily, and placebo pill; 2) sham light and fluoxetine 20 mg daily; 3) combination of light therapy at 10,000 lux, 30 minutes daily, and fluoxetine 20 mg daily; or 4) sham light and placebo pill.
- Montgomery-Asberg Depression Rating Scale (MADRS) was used to measure response and remission periodically during the 8 weeks of this study; other rating scales were used to measure secondary outcomes.
- Combination therapy showed the most statistically significant improvement when compared with sham-placebo, light therapy plus placebo showed some benefits, and fluoxetine plus sham light was not statistically different from placebo.

and continuing the study for a full 8 weeks. Negative ion generators are electrical devices that emit streams of negatively charged ions. In this study, the devices were deactivated and modified to emit a humming sound. Participants were given instructions identical to the group with active light boxes. These conditions were designed to provide credibility; expectation ratings were measured in all groups and found to be quite similar.

The original intent of this study was to enroll 216 patients across six psychiatric clinics in different locations. Lack of participation at several of the centers resulted in a three-clinic study involving 122 patients, all of whom met DSM-IV-TR criteria for MDD.

Pertinent exclusions included comorbid unstable medical disorders, most retinal disorders, and psychiatric disorders (i.e., bipolar, psychosis, or current substance abuse; a seasonal pattern to symptoms; pregnancy; serious risk of suicide; a history of use of light therapy or fluoxetine; and concurrent treatments for depression such as antidepressant use or psychotherapy). In addition, patients whose symptoms spontaneously remitted during an initial week-long period without active treatment were excluded. The 122 patients were randomized to one of the following four treatment arms of the study.

1. Active light box — 32 patients. Fluorescent light box (10,000 lux) and placebo pill: directions were to be exposed to light box 30 minutes each morning.
2. Active fluoxetine — 31 patients. Sham light box (deactivated negative ion generator with audible hum) and fluoxetine 20 mg: directions identical to treatment 1.
3. Sham-placebo — 30 patients. Sham light box (as above) and placebo capsule: directions identical to treatment 1.
4. Combination — 29 patients. Fluorescent light box (10,000 lux) and fluoxetine 20 mg: directions identical to treatment 1.

The Montgomery-Asberg Depression Rating Scale (MADRS) was used to assess response and remission. This scale was chosen due to good inter-rater reliability on telephone evaluations. In this study, telephone evaluations were conducted during weeks 1, 2, 4, 6, and 8. The MADRS is a 10-item scale scored from 0- 60 and is designed to be sensitive to changes resulting from antidepressant use.[3] Remission was defined as a MADRS scale ≤ 10; response was defined as a reduction in MADRS score of at least 50% from baseline. The mean MADRS score at week 0 and mean decrease in MADRS score at the end of 8 weeks for each arm are depicted in Table 1. Table 2 lists the remission and response rates for each arm and the relevant *P* values.

Treatment Emergent Side Effects (TEAE). Each arm of this study had more than 50% of the subjects self-reporting a TEAE. Most were transient symptoms. The dropout rates due to TEAE were similar in each group, leading the authors to conclude that for the most part each intervention was well tolerated.

■ COMMENTARY

There is no point treating a depressed person as though she were just feeling sad, saying, "There now, hang on, you'll get over it." Sadness is more or less like a head cold —

Table 1: MADRS changes week 0 to week 8 and corresponding *P* values

	Mean MADRS week 0	Mean decrease MADRS week 8	*P* values vs sham-placebo
Light box-placebo	27.0	13.4	$P = 0.006$
Sham-fluoxetine	26.6	8.8	$P = 0.32$
Sham-placebo	25.8	6.5	
Combination light box and fluoxetine	26.9	16.9	$P < 0.001$

Table 2: MADRS Response (week 8 MADRS reduced by at least 50 %) and Remission (week 8 MADRS < 10) for each group

	Light-placebo n = 32	Sham-fluoxetine n = 31	Sham-placebo n = 30	Combination n = 29
Percent remission (MADRS ≤ 10 by week 8)	43.8 *$P = 0.27$ vs sham-placebo	19.4 *$P = 0.31$ vs sham-placebo	30	58.6 *$P = 0.02$ vs sham-placebo
Percent response (MADRS reduced at least 50% by week 8)	50 *$P = 0.17$ vs sham-placebo	29 *$P = 0.69$ vs sham-placebo	33.3	75.9 *$P = 0.005$ vs sham-placebo

with patience, it passes. Depression is like cancer.
— Barbara Kingsolver, The Bean Trees

Depression affects an estimated 350 million people worldwide.[4] Untreated depression waxes and wanes but most commonly progresses insidiously with disability, worsening of chronic medical conditions, and even suicide as possible outcomes.[5] Antidepressant medication is a conventional treatment for depression.[6] Poor compliance with long-term use of medications (current recommendations are a 1- to 2-year course of treatment) and patient preference for alternative and adjunct treatment drive the search for less intrusive, more effective, and well-tolerated interventions.

Treatment of seasonal depression with full spectrum light at 30 minutes daily is an accepted intervention for this specific category of affective illness.[1] Using this same intervention for non-seasonal MDD is theoretically interesting but not yet well accepted or tested. The authors claim that this study represents the first well-controlled and appropriately designed study investigating light monotherapy and combination therapy (light and antidepressant medication) in the treatment of non-seasonal MDD.

Several aspects of this cleverly designed study may be useful to explore to better understand and interpret the findings. Notably, the study was designed to include 216 patients at six centers over a period of 3 years. The authors explained that lack of enrollment led to a sizable downgrade to 122 patients at three psychiatric centers. The lower numbers certainly may have affected the findings and lead to some questions regarding validity and specifically the ability of the statistics to detect differences of clinical significance.

Although not a primary focus of this study, it is curious that the sham light-fluoxetine arm was not statistically different from placebo. This is somewhat surprising, as previous studies have documented the efficacy of fluoxetine in treatment of MDD.[7] It may be here that the lower number of subjects was most effective in limiting the ability to detect statistical differences. Of note, other studies looking at antidepressants and placebo have noted a pattern of antidepressant response higher than placebo, primarily in more severely depressed patients and also in studies with multiple antidepressant treatment arms; in other conditions, the antidepressant and placebo rates of response are statistically non-significant, as we see in this study.[8,9]

It is also interesting that the sham light-fluoxetine arm included use of a deactivated negative ion generator with an audible hum. Although there is no indication that this sham-light itself had a negative effect on results, the design of this study cannot allow this to be ruled out. The study used fixed doses of both light and fluoxetine. Tapering up the dose of antidepressant medication in non-responders after week 4 is a typical strategy used in clinical practice; allowing clinically indicated dose changes in the study may have uncovered a more robust response. This may hold true for the non-responders to light therapy as well (although there are no clear medically tested guidelines regarding increasing length of time of light exposure to increase response).

The relatively low-risk nature of light treatment is appealing, especially when compared to the known side effects of antidepressants, which include potential for suicidal thoughts to emerge, libido reduction, weight gain, and sleep disruption.[10] Both medication and light therapy can lead to the emergence of hypomania in

certain patients[11]; vigilance and appropriate follow-up is important in treatment of depression regardless of the modality.

The question remains whether front-line practitioners should prescribe light exposure in addition to (or in place of) antidepressant medication for adult patients with MDD. This study, while interesting and suggestive, does not give clear medical evidence to support this as a first-line or standalone intervention. Further studies clarifying the role of light exposure and mechanism of action in the treatment of depression should help to "shed more light" and provide clear recommendations.

The importance of treating depression in general is not in contention; effective treatment can limit or reverse the natural tendency of MDD to progress. Using evidence-based, safe, effective, and robust treatments remains an essential key in addressing this disorder. Developing new modalities and treatments can advance the field and reduce the morbidity and mortality associated with MDD. For now, it seems reasonable to tell patients with MDD that light exposure may be helpful for treating non-seasonal depression and that there is a potential for additive effect when combined with conventional antidepressant medication. ■

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DEPRESSION

ABSTRACT & COMMENTARY

Exercise for Depression During Pregnancy

By Shahed Samadi, MD, MPH

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Dr. Samadi reports no financial relationships relevant to this field of study.

SYNOPSIS: Exercise is associated with better mental outcomes during pregnancy.

SOURCE: Daley AJ, et al. The effectiveness of exercise for the prevention and treatment of antenatal depression: Systemic review with meta-analysis. *BJOG* 2015;122:57-62.

In this meta-analysis, the authors reviewed randomized, controlled trials to determine whether exercise is an effective intervention for preventing and improving depressive symptoms during pregnancy. Study selection included recruitment of non-depressed pregnant women, at risk or diagnosed with antenatal depression and any exercise intervention. Multiple databases were used for data extraction including: Cochrane Database of Systemic Reviews, MEDLINE, Excerpta Medica database, Allied and Complementary Medicine Database, and PsychINFO with published studies dating from 1946 to February 2014. The authors assessed potential studies for their methodological and reporting quality using the Delphi method, a scale used to assess the quality of randomized, controlled trials. The initial electronic database literature search resulted in a total of 919 articles. Of these, six trials met all inclusion criteria. The main reasons for exclusion were any intervention that did not evaluate depression, trials that did not last more than 6 weeks, or any studies that were not randomized, controlled trials.

The six studies were published between 2008 and 2014 in the United States and Colombia and included 406 pregnant women from 16 weeks' gestation between the ages of 14-38 years. Interventions lasted 8 or 12 weeks, and almost 86% of the participants completed follow up. All trials evaluated exercise as single intervention and used the Centre for Epidemiological Studies-depression scale. Subgroup analyses were performed for women who were not depressed vs those who were depressed or at risk of depression at baseline; the type of exercise

Summary Points

- Six randomized controlled trials show that exercise is both a preventive and treatment of depression in pregnancy.
- Aerobic and non-aerobic exercise had similar effects, though only yoga was studied in women who were depressed at baseline.
- The ACOG guideline still holds: ≥ 30 minutes of moderate exercise is beneficial in pregnant women.

intervention was another subgroup analyzed. One trial evaluated aerobic exercise (walking, running, swimming) and five trials evaluated non-aerobic-based exercise (yoga, tai chi, strength training). All of the trials in the analysis of women depressed at baseline evaluated predominately yoga-based activities. All six trials showed a statistically significant reduction in depression scores with exercise (95% confidence interval [CI], -0.87 to -0.05; $P = 0.03$). The test for subgroup differences in women who were non-depressed and depressed at baseline was not significant ($P = 0.32$; $I^2 = 68\%$). The test for subgroup differences between aerobic and non-aerobic exercise was also not significant ($P = 0.32$; $I^2 = 68\%$). No trials reported data on safety or adverse effects.

■ COMMENTARY

Major depression is one of the most common mental disorders in the United States, and 6.7% of all U.S. adults have had at least one major depressive episode.[1] The burden of depression and other mental health conditions is also on the rise globally, with an estimated 350 million people affected.[2] Depression is the third leading contributor to the global disease burden, and is expected to rise to first by 2030.[3] Women are commonly subjected to psychiatric illness, particularly during pregnancy, and depression is the most prevailing. Depression has been correlated with negative birth outcomes and it has been shown that children are vulnerable to the long-term effects of maternal depression during pregnancy well into adolescence.[4] This is termed intergenerational transmission, which could explain the hereditary risks associated with depression. Researchers have found that children of mothers with a history of depression are five times more likely to have a depressive episode than children of mothers with no history of depression.[5] Thus, finding effective interventions is important for the health of the mother and the newborn.

The benefits of exercise are generally positive, as it applies to many clinical conditions. For example, exercise has a protective effect on health and its benefits are long-standing, such as blood pressure reduction, prevention of coronary heart disease, and long-term glycemic control for diabetics, as adaptations to regular exercise improve insulin sensitivity.[6] A consistent body of evidence also indicates that depression is associated with dysregulated inflammation and release of pro-inflammatory cytokines, which increase the development of metabolic syndrome.[7] The general consensus among the American College of Obstetricians and Gynecologists (ACOG) and the Royal College of Obstetricians and Gynecologists is that exercise is associated with better mental health outcomes during pregnancy. ACOG guidelines suggest that pregnant women without obstetric complications should adopt the same recommendation that was written for non-pregnant women: an accumulation of 30 minutes or more of moderate exercise a day.[8] The Centers for Disease Control and Prevention and the American College of Sports Medicine also recommend at least 30 minutes of moderate-intensity physical activity, defined as 3-5 energy metabolic requirements, for nonpregnant women.[9] This is equivalent to brisk walking at 3-4 mph.

Exercise may be a safer method of treating depression than antidepressants. Use of antidepressants during pregnancy has been increasing in recent years and is estimated to be at 2-6% among pregnant women.[10] Although depression in the general population is approached with both pharmacotherapy and complementary therapies, the disadvantages posed by the use of psychopharmacotherapy are more prominent in pregnant women. Multiple studies have shown an increased risk of pulmonary hypertension[11] or other anomalies such as congenital heart defects[12] with maternal use of selective serotonin re-uptake inhibitors in pregnancy. In fact, they are listed as FDA pregnancy category C in most sources. Furthermore, antidepressants with serotonergic activity are also known to cause mild to severe sexual dysfunction such as decreased libido, delayed orgasm,[13] and even weight gain.[14] A potential link between intellect and behavioral issues with antidepressant use during pregnancy also has been studied as a modifiable causal factor.[15]

Being in a state of depression can be stressful, and vice versa; in these situations, exercise may play a role. For example, stress has been shown to influence increased use of pharmacologic agents, dietary behaviors, and poorer compliance with prenatal care. The intensity, duration, and type of stress can exacerbate depressive symptoms and elevate cortisol levels. Perceived constraints in life, strains in relationships with friends and family, as well as difficulty with finances or job-related demands are some of the most common offending agents. Elevated levels of cortisol can increase one's risk of developing depression and have the potential to predict adverse birth outcomes. In one study, women with low birth weight infants had higher levels of cortisol.[16] Regular exercise has been shown to result in a reduction of circulating cortisol levels. However, studies show that the intensity threshold

also matters and has to be taken into consideration. Low-intensity exercise reduces circulating cortisol levels whereas moderate- to high-intensity exercise provoked increases in circulating cortisol levels.[17]

Expectant mothers could benefit from exercise interventions to improve their physical and mental well being and reduce the risks associated with depression, but this isn't borne out by results presented here. The findings of this meta-analysis are based on a small sample size and, thus, insufficient power; therefore, discretion is vital when interpreting results. Small demographic covariates and a large age gap between participants make it difficult to generalize to all ethnic populations and age groups. Self-reported race/ethnicity, income, body mass index, other medical conditions, marital status, and region of residence (such as in a metropolitan area) may have affected any potential effect modification on the association between depression and exercise during pregnancy. Although depression scores were reduced with exercise, there was no statistically significant difference between aerobic and non-aerobic exercise. Thus, it is difficult to assert what type of exercise, if any, might be most effective, as there is no clear dominance of one form over another. In addition, only two studies elaborated on whether the exercises were performed during exercise classes or at home. Group interventions provide motivational support from fellow staff and participants and thus make adherence more likely; this may explain the high percentage of participant follow-up in the study. This review does provide some preliminary support about exercise as a possible treatment for antenatal depression. However, a clear-cut conclusion about the use of exercise as a preventive measure for depression cannot be made. More high-quality trials are needed to address this question, and to clarify its safety in this population. In addition, while exercise is a viable alternative to standard medications in the treatment of depression, it would be intriguing to look at the long-term effects on the offspring post-intervention. ■

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CANCER

ABSTRACT & COMMENTARY

Antioxidant Therapies: A Contraindication for Melanoma?

By Carrie Decker, ND

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Dr. Decker reports no financial relationships relevant to this field of study.

SYNOPSIS: A series of experiments utilizing human melanoma cells found that oxidative stress was higher in circulating melanoma cells and distant metastasis than the original subcutaneous tumors, suggesting a higher oxidative stress burden subsequent to leaving the original tumor environment. Treatment of animals or tumor cell lines with antioxidants led to increased metastasic burden.

SOURCE: Piskounova E, et al. Oxidative stress inhibits distant metastasis by human melanoma cells. *Nature* 2015;527:186-191.

Human cells from highly efficient (UT10, M481, M405, and M514) and inefficient (M597, M528, M610, and M498) metastasizing melanomas were used for a series of experiments investigating the mechanisms promoting metastasis in animal studies. In the first set of experiments, cells from the highly efficient and inefficient cell lines were injected into mice subcutaneously, intravenously, or directly into visceral organs. Cell lines with known inefficient metastatic potential were found to be associated with much lower levels of distant metastasis with injection subcutaneously, intravenously, and even direct injection into visceral organs, reinforcing clinical observations. However, the inefficient and efficiently metastasizing cell lines did not exhibit a difference in solid tumor formation or growth rate with local subcutaneous injection, suggesting the differences in metastatic potential is due to cellular differences that occur outside the original environment.

In the second set of experiments, the potential reversibility of cellular changes associated with higher rates of metastasis was investigated. Cells from a single melanoma tumor line that had formed subcutaneous tumors, were present in circulation, and had formed liver metastasis were given to recipient mice by subcutaneous, intravenous, or intrasplenic injection in a full factorial experiment. The primary finding of this set of experiments was that the melanoma tumor cells were most likely to form new tumors in the environment from which they were sourced (i.e., cells from a metastatic nodule were most likely to form a tumor when injected in a distant organ, and subcutaneous tumor cells were most likely to form a new subcutaneous tumor).

With a follow-up experiment to investigate if changes were reversible, melanoma cells from subcutaneous tumors, the blood, or liver metastasis were transplanted subcutaneously in recipient mice and allowed to form subcutaneous tumors. Cells from these subcutaneous tumors of differing original sources were then transplanted to a new set of recipient mice by subcutaneous, intravenous, and intrasplenic injection. Cells from all original cell lines formed subcutaneous tumors with high efficiency while metastatic tumors were formed at a very low efficiency. Thus, the changes that the cells experienced leading to their metastatic potential are likely reversible.

Finally, the levels of oxidative stress in melanoma cells and the effect of antioxidant therapies were investigated. In subcutaneous tumors, a significantly higher glutathione to oxidized glutathione ratio was found compared to the circulating melanoma cells (CMCs, $P < 0.05$) and those from metastatic nodules ($P < 0.0005$). Additionally, higher levels of cytoplasmic reactive oxygen species (ROS) were found in CMCs and distant metastatic cells, and higher mitochondrial ROS levels were found in metastatic cells ($P < 0.00005$), suggesting a higher oxidative stress burden in distant locations. A decreased mitochondrial mass was found in the CMCs and metastatic cells. As mitochondrial respiration is a main source of ROS, it suggests this is a mechanism by which the melanoma cells attempt to reduce ROS burden.

To investigate the effect of antioxidants, after subcutaneous transplant of previously metastatic melanoma cell lines, N-acetyl-cysteine (NAC) was given by subcutaneous daily injections at a level of 200 mg/kg/day. NAC treatment did not significantly affect the growth of subcutaneous tumors, but it did increase levels of CMCs with some cell lines as well as metastasis burden with all cell lines tested ($P < 0.05$ to 0.0005, depending on cell line). Pretreatment of efficiently metastasizing melanoma cells with NAC prior to intravenous injection was associated with a tenfold increase in tumor formation ($P < 0.0001$). The combination of these factors suggests oxidative stress plays a significant role in the inhibition of melanoma metastasis.

In addition to these experiments, further investigations of the mechanisms that potentially contribute to glutathione regeneration were performed. Cellular adaptations that may support glutathione levels were found in efficiently metastasizing cell lines, including increased NADPH ($P < 0.05$) and higher levels of the

Summary Points

- A series of experiments using human-sourced melanoma cells were developed to investigate the mechanisms promoting metastasis in vivo in mice.
- Highly efficient melanoma cell lines had low rates of metastasis when injected intravenously (1:235) or directly into visceral organs (variable by organ, 1:173 for intrasplenic injection), while subcutaneous injections led to formation of local tumors at a much higher rate (1:8).
- Mice with subcutaneous melanoma tumors that were treated with daily injections of a known antioxidant, N-acetyl-cysteine (NAC), had an increased metastatic burden.
- Pre-treatment of melanoma cells with NAC prior to intravenous injection increased tumor formation tenfold.

NADPH regenerating enzyme ALDH1L2. Other changes suggested increased utilization of the folate pathway for NADPH regeneration. MTHFD1 also is a NADPH regenerating enzyme in the folate pathway, and gene knockdown studies of ALDH1L2 and MTHFD1 found that both of these enzymes were significant in promoting melanoma metastasis. Finally, treatment with low-dose methotrexate, an inhibitor of dihydrofolate reductase, was found to significantly reduce the frequency of CMCs and metastatic burden, while it did not have a significant effect on the growth of subcutaneous tumors.

■ COMMENTARY

Simply summarizing the rather complex series of experiments, what this study suggests is that a higher oxidative stress burden is, in part, what limits melanoma metastasis, and cells that more efficiently metastasize experience metabolic changes that support their own antioxidant production. Antioxidant treatment of animals and cell lines also promoted metastasis. Although this study investigates only melanoma cell lines, the issues it raises concerning oxidative stress and metastasis are pertinent, as antioxidant therapies are often discussed as part of the treatment and prevention of cancer. Antioxidants are often used to reduce side effects of radiation or chemotherapy by protecting healthy tissues from damage induced by oxidative stress. Administration of antioxidants during radiation and chemotherapy is a controversial issue, as the success of treatments such as these are often based in part on the damage induced by oxidative stress to cancerous cells.[1] The findings of this study lead to additional concerns with the use of antioxidants in the setting of cancer treatment or prevention, as treatment of both the animal and cell with antioxidants increased metastasis significantly.

As oxidative stress is a mechanism by which oncogenic mutations in cellular DNA may occur,[2,3] antioxidants are obviously not something to be avoided at all costs for the purpose of cancer prevention. Oxidative stress within cells and related ROS may even act as secondary messengers, inducing and maintaining the oncogenic phenotype of cancer cells.[4] The oxidative stress associated with radiation therapies for cancer are associated with secondary carcinogenesis.[5] It has been estimated that the cumulative incidence of secondary malignancies could be as high as 20% in patients treated by radiotherapy.[6] In the past, the incidence of radiation-induced secondary malignancies had been underestimated because most patients had a short life expectancy after treatment.

Other studies investigating the use of antioxidant therapies have been neutral or showed benefits with their use as an adjunctive treatment for cancers (including those with metastasis). Intravenous (IV) treatment with alpha-lipoic acid has been used in the setting of pancreatic cancer with metastasis,[7] while IV ascorbic acid has been studied for use in a variety of cancer treatment settings.[8,9,10] Antioxidant therapies have been studied in stage 3 and 4 cancer patients with various malignancies and were shown to reduce reactive oxygen species and serum levels of inflammatory cytokines while increasing glutathione peroxidase activity; however, in this study, the authors did not investigate the effects on outcomes.[11] Lipoic acid also has been studied in clinical trials for the prevention of chemotherapy-induced peripheral neuropathy without significant adverse effects or worsening the outcomes of chemotherapy,[12] while NAC has been used for prevention of cisplatin-induced ototoxicity and oxaliplatin-induced neuropathy.[13,14]

A review pertaining to the use of vitamins, particularly vitamins A, D, E, K, and C, in the setting of melanoma also was recently published.[15] Each of these can have some action as an antioxidant, although vitamin E and C are the ones most often thought of as such. Multiple studies, both in vitro and in vivo, support the use of these nutrients as protective agents or useful for chemoprevention and treatment for melanoma, although the mechanisms by which they may be beneficial vary. However, vitamin C in particular has been shown to support the cellular levels of glutathione, which was shown to have a detrimental effect in the current study.[16] Other compounds with known antioxidant potential, such as green tea catechins,[17] resveratrol,[18] and curcumin,[19] have been studied extensively in the setting of cancer (including melanoma) and have evidence supporting their use, despite also functioning as antioxidants. Finally, the dietary intervention of the Gerson diet, an organic plant-based diet with frequent consumption of raw vegetable/fruit juices, was assessed in a retrospective review of the 5-year survival rates of melanoma patients, and survival rates were considerably higher than what is typical.[20]

This is not the first setting in which antioxidants have been questioned as a therapy. Although many studies show isolated parameter and clinical improvements with antioxidant therapies, other studies associate antioxidants with higher mortality as well.[21] Oxidative stress itself plays an important role in instigating cellular repair and antioxidant transcription.[22] In a recent publication it was shown that cancer risk is potentially 70-90% influenced by extrinsic rather than intrinsic factors.[23] Thus, the potential contribution of oxidative stress associated with carcinogens, infection, and lifestyle choices is also likely high.[24] Although cancer patients typically have higher oxidative stress and lower antioxidant activity, oxidative stress markers have not been associated with survival of terminally ill cancer patients.[25]

As more and more knowledge is gained in the field of oncology through studies such as these to understand the differences between various cancerous cell lines, we can continue to anticipate further specialization of cancer treatment strategies, including nutritional support. Given

the findings of this study, individuals with melanoma, especially those with known metastasis, may want to avoid supplemental antioxidants, particularly NAC, until further research pertaining to the findings of this study can be done. ■

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NUTRITION

SHORT REPORT

Eat Less Sugar: The New National Dietary Guidelines

By David Kiefer, MD, Editor

SOURCE: U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Available at: http://health.gov/dietaryguidelines/2015/guidelines/. Accessed Jan. 10, 2016.

Blanketing the web and airwaves in the first week of the new year were the bullet points "eat less sugar" and "only 10½ teaspoons of sugar daily," the latest of Dietary Guidelines from the U.S. Department of Health and Human Services and the U.S. Department of Agriculture.[1] The guidelines were so much more, and less, than the headlines, and may be the cornerstone for dietary policy during its 5-year lifespan, that it deserves a closer look. Made up of 15 members (MDs and PhDs), the 2015 Dietary Guidelines Advisory Committee reviewed the latest scientific literature in crafting the recommendations, which were "…designed for professionals to help all individuals ages 2 years and older and their families consume a healthy, nutritionally adequate diet." The recommendations strive to expand on previous guidelines by focusing more on *eating patterns* rather than "individual dietary components" (food groups, nutrients).

Five general guidelines and numerous recommendations were contained in the 2015-2020 Dietary Guidelines documented, as listed in Table 1. Under the umbrella

Summary Point

- The 2015-2020 Dietary Guidelines for Americans introduces a new recommendation that added sugar should be limited to no more than 10% of total calories.

of points listed in Table 1 were details such as a recommendation to limit added sugar to 10% of total calories (most people eat double that, approximately 22 teaspoons daily), limit saturated fat intake to < 10% of total calories, limit sodium intake to 2300 mg per day, and consume alcohol in moderation (one drink daily for women, two drinks daily for men) if at all.

The mention of a sugar limit is considered an improvement over previous Dietary Guidelines, whereas the saturated fat and sodium guidelines are unchanged from the past.[2] Critics point out that many of the recommendations continue to be about nutrients and food groups rather than "eating patterns," that calories were de-emphasized, and the guidelines fail to mention that eating less meat or drinking less sugary beverages might be healthy options.[2,3] There may indeed be politics involved in these omissions given the farming and food production dictates in the USDA.[2,3] The health concerns surrounding the intake of red meat, especially processed red meat, are becoming less debatable,[4] so a lack of mention in the current guidelines is arguably problematic.

Will the current guidelines, if followed to the tee, lead to an improvement in the health of Americans? It is difficult to say. The science of nutrition is complicated, and should not be evaluated independent of lifestyle (of note, these guidelines do mention physical activity and the socio-ecological model) nor the myriad of individual risk factors. That said, a strict adherence to a lower sugar intake may improve the incidences of type 2 diabetes and cardiovascular disease, but the guidelines could have, and should have, gone much further to apply the latest research to promoting dietary change in the United States. ■

Table 1: Guidelines and Recommendations, from 2015-2020 Dietary Guidelines

Guidelines
• Follow a healthy eating pattern across the lifespan.
• Focus on variety, nutrient density, and amount.
• Limit calories from added sugars and saturated fats and reduce sodium intake.
• Shift to healthier food and beverage choices.
• Support healthy eating patterns for all.
Recommendations
• Variety of vegetables from all sub-groups
• Fruits (especially whole fruits)
• Grains, half of which are whole grains
• Fat-free or low-fat dairy, and/or fortified soy beverages
• A variety of protein foods
• Oils
• Limit: saturated fats and trans-fats, added sugars, and sodium

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DEPRESSION

SHORT REPORT

Yoga for Prenatal Depression

By William C. Haas III, MD, MBA

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Dr. Haas reports no financial relationships relevant to this field of study.

SOURCE: Gong H, et al. Yoga of prenatal depression: A systematic review and meta-analysis. *BMC Psychiatry* 2015;15:14-22.

The effect of yoga on prenatal depression, one of the strongest risk factors for postnatal depression, was analyzed in a recent systematic review. Studies that randomly assigned pregnant patients to either a yoga therapy group or a non-pharmacological control group were identified for review. No restrictions were placed

on the type of yoga performed or whether all pregnant women enrolled in the studies met DSM-IV criteria for depression.

Six randomized, controlled trials were included for meta-analysis. Three studies involved exercise-based yoga (movement and stretching only), while the other half implemented integrated yoga therapy (exercise along with meditation). Four of the studies enrolled only women meeting DSM-IV criteria for depression, while two studies enrolled depressed as well as non-depressed women.

The results indicated that pregnant women engaging in yoga displayed fewer symptoms of depression than women in non-yoga control groups. These findings were consistent regardless of whether the women met clinical criteria for depression. Additionally, when analyzing the type of yoga therapy implemented, integrated yoga programs demonstrated a significant reduction in depression levels (standardized mean difference [SMD], -0.79; 95% confidence interval [CI], -1.07 to -0.51; $P < 0.00001$), while exercise-based yoga failed to reduce depression levels (SMD, -0.41; CI, -1.01 to -0.18; $P = 0.17$).

Summary Points

- Yoga therapy reduces levels of prenatal depression compared to non-pharmacological treatment programs not involving yoga therapy.
- Yoga therapy integrating meditation and relaxation practice improve depression levels more than exercise-only yoga therapy.

Yoga therapy, particularly forms integrating meditation and relaxation practice, demonstrate potential in the management of prenatal depression. Successful non-pharmacological methods for managing prenatal depression should be implemented whenever possible given the risks for antidepressant therapy during pregnancy. ■

LOW BACK PAIN

SHORT REPORT

Acupuncture for Acute Low Back Pain in the Emergency Department

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Dr. Haas reports no financial relationships relevant to this field of study.

SOURCE: Liu Y, et al. Efficacy and safety of acupuncture for acute low back pain in emergency department: A pilot cohort study. *J Evid Based Complementary Altern Med* 2015;2015:179731.

Researchers in Taiwan evaluated the safety and efficacy of acupuncture therapy for managing acute low back pain (LBP) treated in an emergency department. Sixty patients experiencing acute LBP without a life-threatening condition or severe neurological deficit were divided into two groups based on their willingness to receive acupuncture. Both the acupuncture and the control groups underwent a one-time treatment for 15 minutes at fixed points (LI10, L14, ST36, GB34, LR3). Of note, acupuncture therapy frequently involves individualized points as opposed to the fixed points performed in this study. Sham treatment was applied to the control group using seed patches (cluster of small seeds fixed to the skin with adhesive tape). The primary outcome was LBP scores measured using a visual analog scale at baseline, immediately after treatment, and day 3 post-treatment. Adverse events were recorded as secondary outcomes.

Summary Point

- Acupuncture may reduce acute low back pain among patients treated in the emergency department.

No significant differences between the two groups were noted at baseline. Immediately after the intervention, only the acupuncture group experienced a significant decrease ($P < 0.001$) in pain; however, 3 days after treatment both groups experienced significant pain reductions (acupuncture, $P < 0.001$; control, $P < 0.011$). No significant adverse events were reported in either group. Although limited by the inherent shortcomings of

a cohort study, the present study offers encouraging results regarding acute LBP, one of the most common complaints among patients in the emergency department. Before drawing definitive conclusions, additional studies should be performed with larger sample sizes, randomization, and blinding between the groups. Further characterizing the patients that experience the greatest improvement in LBP should also be performed due to the complex nature of pain management, whether acute or chronic. ■

CME INSTRUCTIONS

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CME QUESTIONS

1. **In the article discussing the use of light therapy for treatment of non-seasonal major mepressive misorder (MDD), which of the following statements is true?**
   a. Regulated exposure to full spectrum light is as effective for nonseasonal MDD as it is for Seasonal Affective Disorder (SAD.)
   b. Patients showed equal improvement in symptoms of MDD (response or remission) when treated with light therapy alone or a combination of light therapy and fluoxetine, but not with fluoxetine alone.
   c. Patients demonstrated the most statistically significant improvement in symptoms of MDD when treated with fluoxetine and full spectrum light therapy.
   d. Patients in the sham light-placebo arm of this study showed a response rate similar to the active combination of full spectrum light and fluoxetine.
2. **Most individuals accept that stress is harmful, particularly with the surge of the stress hormone cortisol. Regular exercise has been shown to result in a reduction of circulating cortisol levels. At what intensity of exercise has been shown to decrease cortisol levels?**
   a. Mild to moderate intensity
   b. Moderate to high intensity
   c. Low intensity
   d. High intensity
3. **In the in vivo animal model of human melanoma metastasis, subcutaneous daily injections of N-acetyl-cysteine was shown to:**
   a. increase subcutaneous tumor size but reduce the burden of metastasis.
   b. increase subcutaneous tumor size and the burden of metastasis.
   c. not affect the subcutaneous tumor size but increase the burden of metastasis.
   d. reduce the subcutaneous tumor size and the burden of metastasis
4. **Which of the following is true regarding the 2015 Dietary Guidelines?**
   a. It is recommended to have no added salt.
   b. Saturated fat plus trans fat should equal no more than 20% of total calories.
   c. A limit of alcohol intake of two drinks for women and one drink for men is mentioned.
   d. Added sugar should be limited to no more than 10% of total calories.

[IN FUTURE ISSUES]

- Integrative therapies for dementia
- Mediterranean diet and breast cancer
- Alexander technique and chronic neck pain
- Coffee consumption and mortality