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HYPERTENSION

ABSTRACT & COMMENTARY

The Risks of a Low-salt Diet: A Meta-analysis

By David Kiefer, MD, Editor

SYNOPSIS: This meta-analysis of four large prospective cohort studies indicates that people with or without hypertension are at increased risk of death or cardiovascular events when consuming low amounts of sodium. In addition, people with hypertension may be at increased risk of such events with high-sodium intake.

SOURCE: Mente A, O'Donnell M, Rangarajan S, et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: A pooled analysis of data from four studies. *Lancet* 2016; May 20. pii: S0140-6736(16)30467-6.

There were some whisperings in the literature that a generalized suggestion of lowering salt intake may not be universally beneficial. The thought is that there may be risk for cardiovascular disease or mortality at both high and low dietary sodium consumption, but that this risk may be moderated or increased by cofactors such as coexisting hypertension. This large epidemiological study aimed to delve further into this issue to determine the most appropriate clinical salt-related dietary recommendations for specific demographics.

The authors used information from four studies on a total of 133,118 individuals, including 63,559 with hypertension and 69,559 who were normotensive. One of the included studies, a large cohort study, is called the Prospective Urban Rural Epidemiological (PURE) study, which enrolled 156,424 people, aged 35-70 years, in both rural and urban low-, middle-, and high-income communities on five continents. For 101,511 of these study participants, morning and fasting urine samples were available, as were baseline blood pressure measurements. Another study, called EPIDREAM, was a prospective cohort trial of 17,453 individuals, aged 18-85 years, who were followed long-term and some of whom were included in a pharmaceutical randomization trial. Out of the EPIDREAM cohort, the authors of the current trial analyzed those who developed cardiovascular disease (n = 478) and a match control cohort (n = 2372). In addition, this

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Summary Points

- This is a meta-analysis of 133,118 study participants looking for all-cause mortality and cardiovascular events, the primary outcomes.
- The risk of such events was analyzed adjusting for hypertension status and estimated urine sodium excretion, the latter meant to approximate dietary sodium intake.
- Study participants with low urine sodium excretion were at increased risk of the primary outcomes, regardless of hypertension status.
- Only those study participants with hypertension were at risk of death or a cardiovascular event if they had an elevated urine sodium excretion.

analysis included 28,757 study participants from TRANSCEND (a randomized, placebo-controlled trial on telmisartan) and ONTARGET (a randomized, controlled trial on telmisartan, ramipril, and combination therapy).

For all study participants, a fasting morning urine sample was collected and analyzed for an estimate of 24-hour urinary excretion of sodium and potassium. The authors cited research supporting that this measurement reliably approximates sodium intake in both healthy and hypertensive individuals. Furthermore, weight, height, and two blood pressure measurements were recorded, with a value > 140/90 mmHg defined as hypertensive, as well as confounding variables such as gender, body mass index, education level, alcohol use, smoking status, and geographic location. The analyses included a multivariable linear regression analysis for the effect of estimated sodium excretion on blood pressure and a restricted cubic-spline plot to delineate the association between estimated sodium excretion and the primary outcome, a composite of death, myocardial infarction, stroke, and heart failure. Hazard ratios (HR) of time to event were calculated using Cox proportional hazard models with shared frailty models.

The mean estimated urinary sodium excretion was 4,956 grams per day in those with hypertension, compared to 4,823 grams per day in those who were normotensive, a statistically significant difference ($P < 0.0001$). The distribution of estimated urinary sodium excretion values is shown in Table 1. All told, 11,146 (18%) of the hypertensive participants and 10,094 (15%) of the normotensive participants were in the low (< 3 grams daily) or high (> 6 grams daily) tertiles of estimated urinary sodium excretion, a significant difference ($P < 0.0001$).

In individuals with hypertension, 6,835 (11%) had a cardiac event or all-cause death (the primary outcome); only 3,021 (4%) of those without hypertension had such an outcome. Further analysis showed that whether urine sodium excretion was associated with the primary outcome depended on the hypertension status in what the authors called a "U-shaped" fashion, or increased risk (HR) at low or high urine sodium excretion. For example, in the hypertensive participants, the HR for a urine sodium excretion < 3 grams daily was 1.34 ($P < 0.001$) and > 7 grams daily was 1.23 ($P < 0.001$). In contrast, in the normotensive participants, the HR for a urine sodium excretion < 3 grams daily was 1.26 ($P < 0.009$) but > 7 grams daily was not significant at 0.90 ($P = 0.25$).

Table 1: Distribution, in Number of People and Percentage, of Estimated Urinary Sodium Excretion Values in Hypertensive and Normotensive Study Participants

Estimated urinary sodium excretion	< 3 grams per day	3-6 grams per day	> 6 grams per day
Hypertensive participants	7,006 (11%)	41,427 (65%)	15,126 (24%)
Normotensive participants	7,574 (11%)	47,914 (69%)	14,098 (20%)

■ COMMENTARY

This robust study casts doubt on our blanket recommendation of a low-salt diet for everyone.[1] If we believe that the estimates here based on urine sodium excretion (and the authors provided data to draw a correlation between urine and dietary sodium/salt), then there actually seems to be an increased risk of all-cause mortality or cardiovascular events with sodium excretion/intake < 3 grams daily, as well as for > 6-7 grams daily (only for hypertensive individuals). The concern for public health initiatives aimed at lowering global sodium intake (thought to be beneficial through the lowering of blood pressure) is that there often is not the consideration of hypertension status, which, in this case might be irrelevant (both groups are at risk), or other variables. A simple fix indeed may be too simple and carry risks when generalized to the whole population.

The authors mention that their analysis found 95% of the world's population ingests > 3 grams of sodium daily, whereas only 22% consume > 6 grams daily. They claim that their data supports a benefit in reducing sodium intake in those with high intake **and** hypertension, but it may be problematic to lower sodium intake in other individuals. So, there are little data to support lowering sodium intake in everyone. Again, the harms of blanket statements and recommendations.

The mechanism of this activity is complicated. Statistical analyses not discussed above removed blood pressure levels from the final calculations and still found a sodium association. This could possibly indicate an effect of sodium on physiology (suggested by the authors to be mediated by the renin system) independent of blood pressure effects. These systems are complicated, an obvious statement that prudently directs clinicians to be wary in our recommendations and perturbations to our patients' homeostasis.

As *Integrative Medicine Alert* reviews often comment, an observational, cohort, prospective study such as the four reviewed here cannot comment on causality, but rather merely note an association between sodium intake and the primary outcomes detailed here. A randomized, controlled trial would be necessary for clinicians to confidently counsel our patients to consume a certain amount of sodium daily for a known benefit to disease risk. Until then, what do we do? Try to estimate sodium intake, cardiovascular disease risk, and establish hypertension status. If all three are elevated, there seems to be benefit to lowering sodium intake below 7 grams daily, approaching 3 grams daily. However, patients should be wary of an intake that is "too low" (< 3 grams daily?) until a controlled clinical trial provides further guidance. ■

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DIET

EDITOR'S NOTE

FDA Nutrition Facts Label Changes

By David Kiefer, MD, Editor

SOURCE: FDA. Changes to the Nutrition Facts Label. Available at: www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm385663.htm. Accessed June 15, 2016.

Occasionally, there is current, hot-off-the-press information that is relevant to the readers of *Integrative Medicine Alert* but nonetheless doesn't fit the traditional genres of review article, abstract & commentary, or short report. We feel that it is important to share these pearls with you, and may use "Editor's Note" as such a medium.

On May 20, 2016, the FDA announced changes to the nutrition facts panel required as a label on all foods. There were some cosmetic changes, such as making serving size and servings per container more visible and easier to read, an important feature that perhaps will address the confusion surrounding the number of servings in a package and help to prevent overeating. Another detail is the new requirement to list vitamin D, calcium, iron, and potassium in actual milligrams (or micrograms), not just as percent daily value. To see vitamin D listed in micrograms might be confusing for some people because recommendations and media reviews refer to vitamin D in international units. Another telling change is that "added sugar" has its own line, a new feature that may or may not help consumers improve food choices (some foods "naturally" contain large amounts of sugar; is the label recommending that these are OK?).

In addition, serving sizes have been adjusted to reflect what people are actually eating, and this may be smaller or larger than it was before. For example, one serving of soda is 12 ounces (not 8), and there are only three servings (not 4) in a pint of ice cream. In theory, the

serving size change will increase the calories per serving and, hopefully, affect people's decision-making about the quantity of food consumption. However, it does not help to downshift the oversized eating that is part of the U.S. food crisis; it almost seems to validate it. We will have to see how this all plays out with food decision-making. On this topic, the label also will require two columns of information if there is more than one serving size in a package, one set of information for one serving, and the other column for those instances when the consumer eats the whole package (sound familiar: Doritos, ice cream, etc.?). Another layer of complexity is tied to the question of whether consumers will understand or correctly use this information.

Change is good, especially in the realm of U.S. eating habits and nutritional malaise. Will these label changes help or contribute to the confusion? It remains to be seen, but healthcare providers should be aware of the new label so they can answer patient questions and provide nutritional counseling and health promotion advice to patients in clinic. ■

MIGRAINE

ABSTRACT & COMMENTARY

Combination of Simvastatin Plus Vitamin D Offers New Hope for Migraine Prevention

By Concepta Merry, MB, BCh, BAO, BA

Associate Professor, Global Health, School of Medicine, Trinity College Dublin; Integrative Medicine Fellow, University of Arizona, Tucson

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

SYNOPSIS: A well-conducted, randomized, placebo-controlled trial has shown that the combination of simvastatin (20 mg twice daily) plus vitamin D3 (1,000 international units twice daily) is effective in the prevention of headaches in adults with episodic migraine.

SOURCE: Buettner C, Nir RR, Bertisch SM, et al. Simvastatin and vitamin D for migraine prevention: A randomized, controlled trial. *Ann Neurol* 2015;78:970-981.

Migraine headaches are a leading cause of disability worldwide.[1] Unfortunately, the natural history of migraine is that the headaches tend to become more frequent and more severe with advancing age. Prevention of migraine relies on avoidance of known triggers and prophylaxis with agents such as beta-blockers, tricyclic antidepressants, and anticonvulsants.[2] An integrative health approach also might include butterbur or riboflavin in the prophylactic armamentarium.[3] Despite all of this, some people continue to suffer from debilitating migraine headaches.

A double-blind, randomized, placebo-controlled trial showed that the novel combination of simvastatin plus vitamin D is safe and effective at preventing migraine headaches. The rationale for the new study was two-fold. First, there is a possible biological explanation for the clinical effect. Migraine headaches are associated with endothelial dysfunction and inflammation. Statin therapy has an established role in modulating endothelial dysfunction.[4] Vitamin D acts synergistically with statins to exert an anti-inflammatory effect.[5] Vitamin D also modulates the musculoskeletal pain associated with statin therapy.[6] Second, a previous study conducted by the same research group showed a favorable effect of statin therapy plus vitamin D in migraine.[7]

Summary Points

- A double-blind, randomized, placebo-controlled trial showed that the combination of simvastatin plus vitamin D is safe and effective at preventing migraine headaches.
- No significant side effects attributable to the prescribed medication (including muscle pains) were noted.

The new study recruited 57 adults with a history of at least three years of episodic migraine living in the Boston area. Baseline data were collected over an initial 12-week period. Participants were randomly allocated to either take simvastatin 20 mg twice daily plus vitamin D3 1,000 international units twice daily or matching placebo. Study participants in both groups continued their usual abortive and prophylactic migraine management. Adherence was measured by pill counts and changes in low-density lipoprotein cholesterol measurements in the active group. Study participants kept a detailed migraine diary throughout the study period. The study participants were followed over a 24-week period.

The good news for migraine sufferers is that the treatment group had a significant reduction in the number of migraine days ($P < 0.001$). The active group used abortive medication on fewer days ($P < 0.001$) and used fewer doses of these medications ($P < 0.001$) as compared with their own baseline. Interestingly, there was no significant change in either group compared with baseline in terms of the symptoms associated with migraine such as the migraine severity, migraine duration, or the proportion of headaches that occurred with throbbing, photophobia, or nausea. In effect, there was no benefit in terms of severity or duration once the migraine headache took off. Finally, the combination treatment had a good safety profile, and no significant side effects attributable to the prescribed medication (including muscle pains) were noted.

■ COMMENTARY

Migraine headaches can negatively effect quality of life. This study is likely to be welcomed by migraine sufferers, their families, coworkers, and health care providers. Essentially, the novel combination of simvastatin with vitamin D was effective in preventing migraine headaches and was well tolerated. It is worth noting that the study sample size was small, but this is balanced to some degree by the fact that the study was well conducted. Another plus for the study results is the fact that statin and/or vitamin D therapy have other health benefits, especially for people who live in northern climates. Theoretically, the benefits seen in the study with simvastatin could reasonably be expected to extend to other statins too, but it is hard to say for sure at this stage.

The current study was not powered to evaluate the relative contributions of the statin alone vs. vitamin D alone vs. the combination. Finally, it is worth mentioning that the primary investigators have filed a patent for the combination of a statin plus vitamin D for migraine prevention. The eternal optimist in me takes this not as a conflict of interest but as a sign that the investigators really believe in the benefits of their study.

The downfall of the study from an integrative health perspective is the fact that there was no mention of integrative therapies. This needs to be factored in when thinking about introducing the results of this study into patients who are using complementary therapies for migraine. A practical approach might be to monitor liver function tests in people taking butterbur with pravastatin, as both agents can cause clinically significant rises in liver function tests.[8] The bottom line is that this is definitely worth a try. ■

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HYPERTENSION

ABSTRACT & COMMENTARY

Improving Blood Pressure Through Enhanced Sleep

By William C. Haas III, MD, MBA

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

SYNOPSIS: The use of a benzodiazepine hypnotic among hypertensive patients was associated with improvements in both sleep scores and blood pressure.

SOURCE: Li Y, Yang Y, Li Q, et al. The impact of the improvement of insomnia on blood pressure in hypertension. *J Sleep Res* 2016; [Epub ahead of print].

Summary Points

- Hypertensive patients taking estazolam achieved greater improvements in sleep scores compared to patients taking placebo.
- The use of estazolam was associated with a 10.5 mmHg and 8.1 mmHg reduction in systolic and diastolic blood pressure, respectively, after three weeks of treatment.

The relationship between disordered sleep patterns and increased cardiovascular morbidity and mortality is widely underappreciated, especially in the primary care setting. Several studies have documented an increased risk for developing hypertension among those with poor sleep patterns.[1,2] Moreover, insomnia has been associated with substantial elevations in blood pressure among those already diagnosed with hypertension.[3] Unfortunately, despite these negative correlations, few studies have evaluated the effect of improving sleep on blood pressure control.

Through a conventional pharmacological intervention, a group of Chinese researchers recently attempted to evaluate whether treating insomnia could effectively lower blood pressure in a group of hypertensive patients. Using standard diagnostic criteria established by the World Health Organization for hypertension and insomnia, 566 patients with both disorders were recruited from either an outpatient sleep center or an inpatient geriatric ward. Patients were permitted to participate in the study if currently treated with antihypertensive medications; however, they were excluded if currently taking hypnotics, antipsychotics, or antidepressants. Additional exclusion criteria included diagnosis of sleep apnea, drug/alcohol addiction, chronic renal failure, or a Hamilton Depression score > 16. A total of 403 patients met criteria for participation and 402 completed the study.

As a part of the intervention, patients were randomized in a double-blind fashion to receive either Prosom (estazolam) or placebo for 28 days. Estazolam was started at a dose of 1 mg nightly and adjusted upward to 2 mg on day four based on patient-perceived efficacy — only 21 patients increased to 2 mg per night. The antihypertensive medications used by the patients during the study were long-acting drugs dosed once-daily in the morning and were not changed throughout the study. Blood pressure was measured every seven days for four weeks according to measurement guidelines issued by the World Health Organization.[4] Sleep patterns were assessed along the same time line using the Pittsburgh Sleep Quality Index (PSQI). Patients were also interviewed weekly to follow the use of approved medication (estazolam, placebo, antihypertensives) and restricted medication (antipsychotics, antidepressants, non-issued hypnotics, caffeine).

With regard to sleep outcomes, the global PSQI scores for patients receiving estazolam improved within seven days of treatment and reached nearly 50% improvement by day 28 (18.2 ± 4.9 to 9.3 ± 3.3; $P < 0.001$). Moreover, scores for all the individual PSQI components, including sleep latency, sleep efficiency, and sleep duration, improved in the treatment group after four weeks ($P < 0.001$), while the control group only noted improvements in sleep latency. Overall efficacy of insomnia treatment, as determined by ≥ 50% reduction in PSQI global score, occurred in 63.7% of patients in the estazolam group and only 14% of patients in the control group ($P < 0.001$).

Blood pressure demonstrated a similar pattern of improvement. After the third week, the Estazolam group noted significant reductions in blood pressure, and achieved a 10.5 ± 3.9 mmHg and 8.1 ± 3.6 mmHg reduction in systolic and diastolic blood pressure, respectively ($P < 0.001$). The control group did not achieve significant reductions in either systolic or diastolic blood pressure during the intervention.

■ COMMENTARY

Li and colleagues have conducted one of the few studies pertaining to the effect of sleep enhancement on blood pressure control among hypertensive patients. The researchers found that treatment with a benzodiazepine hypnotic (estazolam) resulted in improved sleep patterns, while effectively reducing daytime blood pressure. The study was generally well designed with only minor limitations. The setting of patient recruitment, particularly the inpatient geriatric unit, may have enhanced results due to artificial disturbances in sleep patterns that commonly occur in the inpatient setting and in that age group. Furthermore, recruiting patients from different settings also may have limited the external validity of the study without specifically analyzing the effect of treatment setting. Regardless of these shortcomings, the present study highlights the importance of addressing sleep disorders among hypertensive patients.

From an integrative medicine perspective, the present study was not chosen in an attempt to promote hypnotics in hypertensive patients with insomnia. Rather, the study was reviewed to draw attention to the importance of sleep in patients with comorbid conditions such as hypertension. Sleep disorders are highly prevalent in the United States, with an estimated 30-40% of the population experiencing inadequate sleep.[5] Unfortunately, primary care providers routinely forget to screen for sleep disorders when conducting a health

history.[6] Before sleep disorders can be addressed, they must first be identified.

In addition to raising awareness, hopefully, this study will spur new research regarding integrative treatments for sleep disorders among hypertensive patients. The current body of literature supporting integrative approaches for improving blood pressure through sleep enhancement is generally lacking. One study evaluating prolonged-release melatonin failed to note improvements in blood pressure compared to placebo.[7] On the other hand, another small study implementing twice daily acupressure for four weeks found in significant improvements in PSQI scores as well as systolic and diastolic blood pressure.[8] Additional research demonstrating a connection between integrative treatment modalities and concurrent improvements in sleep and blood pressure are needed.

Until additional research emerges, practitioners should continue to screen for sleep disorders and review strategies to promote adequate sleep. Safe and effective sleep hygiene recommendations should start with enhancing the sleep environment to ensure the bedroom is cool, quiet, and dark. Encourage patients to reduce excessive "mind noise" through a meditative or journaling practice before bed. Recommend eliminating disrupters of the body's natural circadian rhythm, such as television and/or computers, within the hour before bedtime. These strategies may or may not improve blood pressure as a result of improved sleep, but they will certainly help disordered sleep patterns in a non-habit forming manner. Ultimately, the present study should not be viewed as a nod for benzodiazepines use; rather it should generate a renewed focus on integrative sleep modalities. ■

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AUTISM

ABSTRACT & COMMENTARY

Integrative Approaches to Caring for Children with Autism

By Ellen Feldman, MD

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

SYNOPSIS: Selected treatments for autism spectrum disorder are reviewed and placed into one of four categories (ranging from recommend to avoid) with a goal of creating a practical blueprint for the medical practitioner.

SOURCE: Klein N. Kemper KJ. Integrative approaches to caring for children with autism. *Curr Probl Pediatr Adolesc Health Care* 2016;46:195-201.

"We know what we are, but know not what we may be."

Shakespeare, Hamlet

Autism spectrum disorder (ASD) is aptly named. Symptoms emerge in very early childhood with varying degrees of severity. Shared core diagnostic criteria include functional impairment due to social communication deficits, inflexibility, and unusual levels of reactivity to sensory input sometimes leading to agitation or outbursts. Intelligence levels range from intellectual impairment to extremely gifted. Despite shared characteristics, this disorder truly exists on a spectrum from mild impairment with need for little intervention to severe impairment with need for lifetime support. The diversity of clinical presentation

Summary Point

- These authors reviewed some of the more common treatments for autism spectrum disorder and place each into one of four categories to guide the medical practitioner when faced with choosing an intervention for a person with autism spectrum disorder.

is mimicked by diversity of intervention — treatment is targeted toward reduction of symptoms, as there is no "cure" or identified single causative agent of ASD.[1]

The CDC estimates that one in 68 children in the United States are diagnosed with ASD. These numbers hold true across racial and socioeconomic groups, but differ according to gender, as ASD is about 4.5 times more common in boys than in girls.[2] With limited medical interventions available and with concern about timely intervention in young children, up to 85% of families affected by this disorder pursue complementary or alternative remedies.[3,4]

Noting this trend, Klein and Kemper reviewed some of the more common treatments for ASD and place each into one of four categories: recommend, monitor, tolerate, or avoid. These groupings are meant to guide the medical practitioner when faced with choosing an intervention for a person with ASD. The authors remind those treating children with ASD that each child is an individual and that even the recommended treatments may not work for every person with ASD. Treatment and interventions need to be re-evaluated and reassessed over time, with consideration of the effect of environmental changes (for example, if a child is entering a new school or classroom) and stages of development at each visit.

■ COMMENTARY

This section lists the categories created by Klein and Kemper, as well as the interventions they placed within each category. I have provided some background and thoughts regarding clinical application of each intervention.

RECOMMEND: ROBUST EVIDENCE OF EFFICACY AND SAFETY

To be placed in this category, Klein and Kemper stipulated that safety and effectiveness must be supported by at least two randomized, clinical trials (RCT) with adequate number of subjects or a systematic review.

1. *Healthy lifestyle*: Address exercise, nutrition, sleep, and social interaction, and avoid neurotoxins. This can be challenging in children with ASD who often demonstrate a "limited food repertoire," leading to risk of nutritional deficiencies. Parental education and instruction regarding behavioral techniques can be useful to help achieve nutritional balance. Behavioral interventions noted below can be used to encourage a wider variety of foods or supplements can be used.[5]

Prenatal vitamin supplements may help with prevention (see vitamin section.)

2. *Applied behavior analysis (ABA) and parent implemented training (PIT)*: ABA is a type of behavioral intervention often conducted in an intensive manner with young children. ABA-trained therapists identify target behaviors and then design specific interventions aimed at improving social skills and teaching cooperative play, self-care, and communication using reinforcement and other behavioral techniques. There is evidence that applications of ABA as early as toddler stage of development are useful in ASD. PIT is an extension of ABA using parent assistance to extend and reinforce concepts. Each of these may be covered by insurance.[6,7]

A 2012 Cochrane review examined evidence for early intensive behavioral intervention (therapies based on ABA) for treatment of ASD in young children. The conclusion was that while there is some evidence of effectiveness, more well-designed studies are needed.[8]

3. *Melatonin*: More than 50% of children with ASD have sleep problems. Melatonin (1-3 mg oral) can be used to address sleep when these problems interfere with daytime functioning. Sleep hygiene should be addressed with or without use of melatonin.[9]

4. *Music therapy*: An updated 2014 Cochrane review concluded that music therapy delivered by a trained music therapist (individually or in small groups) has clear benefit in ASD at least in the short- to medium-term. Advancement of social skills as well as communication in children with ASD are noted.[10]

5. *Neurofeedback*: This is a type of biofeedback that uses EEG information to help children with ASD learn to self-regulate. Electrodes are placed on a child's scalp; brainwaves are represented in a concrete manner (such as a floating ball or color) designed to allow a child to affect change. Subsequent steps link the feedback to behavior. Although there are a few promising studies, cost limits the use of this intervention, which insurance rarely covers.[11]

MONITOR

The few interventions in this category have evidence for efficacy coexisting with concerns about safety, toxicity, or cost.

1. *Risperidone (Risperdal) and aripiprazole (Abilify)*: These medications are FDA-approved to treat children older than 6 years of age for severe aggression and

agitation in ASD. Dosages range according to severity of symptoms, but a good general principal is "start low and go slow." Side effects include metabolic syndrome, weight gain, development of diabetes, tardive dyskinesia, and sedation. Baseline lipid profile, fasting glucose monitoring, and frequent reassessment (monthly in some cases) for efficacy and development of side effects is recommended.[12]

2. *Restrictive diets*: Gluten-free/casein-free has benefits in treatment of comorbid gastrointestinal difficulties. Side effects noted by the authors include poor nutrition if the diet is not well structured; authors advise use of a registered dietician to assist with this intervention.[13]

TOLERATE

Limited medical evidence supporting efficacy; overall are safe and/or low cost; use while research continues.

1. *Dietary supplements*

Omega-3 fatty acids: Studies show mixed results in reducing irritability and aggression associated with ASD and more consistently positive results in improvement of mood. Doses typically used are 1.5 grams/day (0.84 g/d eicosapentaenoic acid, 0.7 g/d docosahexaenoic acid.) The authors noted that more studies with more subjects may allow omega-3s to be moved to recommended category.[14]

Vitamins B6, folate, B12: There have been several reports of above-average serum levels of homocysteine in some children with ASD. Vitamins B6, folate, and B12 act as co-factors to the enzymes needed in homocysteine metabolism. Studies are underway to see if supplementation reduces homocysteine levels in children with ASD and if there are associated changes in behavior.[15]

Use of folic acid in pregnant mothers is associated with a reduced risk of ASD in offspring; studies look favorable for supplementing alpha omega-3, iron, and iodine in pregnancy.[16]

Vitamin C: High-dose (110 mg/kg) ascorbic acid supplementation is supported in preliminary studies to reduce irritability in children with ASD.[17]

Vitamin D: Insufficiency and deficiency are commonly found in children with ASD; preliminary studies are favorable regarding correlating supplementation with symptom improvement.[18]

Combined vitamin/mineral supplement: An RCT involving patients with ASD showed statistically significant improvement in both metabolic status and several measures of ASD symptoms following a three-month period. This is perhaps the most rigorous and convincing study thus far linking ASD symptom reduction to nutritional health.[19]

2. *Occupational therapy (including sensory integration)*: Occupational therapists develop and improve practical skills via play-assisted therapy, cognitive-behavioral therapies, or parent-supported therapies. Sensory integration includes techniques such as brushing, swinging, and pressure and may be used within a school setting. Small studies have produced mostly favorable results; implementation can be difficult without available resources (such as trained therapists).[20]

3. *Animal-assisted therapy*: The authors noted that some small studies support equine-assisted activities and therapies. There is speculation that the effect is derived from physical impact (pressure sensation similar to massage) and/or from an emotional impact involving non-verbal communication.[21]

4. *Yoga*: Two recent studies examined teaching yoga techniques to children with ASD to aid in management of disruptive behavior. One 2012 study looked at a manualized form of yoga designed for classroom use and the other study looked at a combination of yoga, dance, and music therapy. Although results are impressive, the study designs do not allow clear conclusions regarding the specific efficacy of the yoga intervention.[22,23]

5. *Massage*: A 2011 review study looked at 132 published studies regarding any type of massage in ASD. Only six of these studies met criteria for inclusion in the review. Results of these six studies linked massage with improvement in several measures of ASD, but none of the trials were sufficiently non-biased to allow firm conclusions.[24]

6. *Chiropractic manipulation*: A 2011 review article concluded there is simply not enough research to form a conclusion regarding the effectiveness of chiropractic manipulation in the care of ASD. There are a few case studies that point to favorable results, and the authors' note this intervention is generally supported by insurance.[25]

7. *Acupuncture*: Two review articles (2011, 2012) looked at acupuncture in ASD treatment. Both found multiple studies reporting improvement in measures of ASD with acupuncture; however, the variability of the studies, including acupoints used and treatment duration, limit conclusions and point to the need for more rigorous studies.[26,27]

8. *Transcranial magnetic stimulation (TMS)*: Strong, rapidly alternating magnetic currents stimulate specified areas of the brain. There are about eight small trials of TMS in ASD (more commonly TMS is used in

treatment-refractory depression); it remains considered an experimental treatment in ASD.[28]

AVOID

These lack evidence of efficacy and have high cost and/or risk.

1. *Hyperbaric oxygen*: Studies show no evidence of consistent improvement in symptoms of ASD and treatment is quite expensive.[29]

2. *Chelation*: Chelation has been proposed as a way to excrete heavy metals that may worsen symptoms of ASD. According to a 2015 Cochrane review, "no clinical trial evidence was found to suggest that pharmaceutical chelation is an effective intervention for ASD." The same reports noted the risk of adverse effects from this procedure are significant and include renal and hepatic toxicity.[28] There are no studies confirming that heavy metal burden worsens ASD symptoms.

3. *Secretin*: A hormone released in the gastrointestinal tract, secretin has been studied in the treatment of ASD after several promising case studies were reported in the late 1990s. A comprehensive 2011 review article found seven RCTs, none of which supported effectiveness of secretin in the treatment of ASD.[31]

CONCLUSION

Treating a child with ASD is complex. The wide variability in type and severity of presenting symptoms, the potential disabling features of the symptoms, and the limited research regarding efficacy and safety of various interventions make treatment difficult. Often a decision to treat symptoms becomes a judgment call weighing the relative effect of functional impairment against the risk associated with intervention. Yet, a successful intervention can be extraordinarily effective in helping a child operate, grow, and learn within a school and family setting. Recognizing the stakes, many families turn to integrative techniques to maximize the potential and aid their affected child navigate a complex world. Knowing and understanding the research is invaluable when assisting families in their quest to make an informed decision regarding intervention. ■

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SHORT REPORT

Integrative Treatment for Restless Legs Syndrome: What Does the Evidence Say?

By Ellen Feldman, MD

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

SYNOPSIS: Medical evidence supports the use of physical activity and iron supplementation (for those with low serum ferritin) in patients with restless legs syndrome.

SOURCE: Bega D, Malkani R. Alternative treatment for restless legs syndrome: An overview of the evidence for mind-body interventions, lifestyle interventions, and neutraceuticals. *Sleep Med* 2016;17:99-105.

Restless legs syndrome (RLS) is a neurologic disorder occurring in 10-40% of adults. An uncomfortable sensation to move limbs while at rest and relief from symptoms with movement is pathognomonic of RLS; treatment is not as clear-cut. Use of conventional agents, such as benzodiazepines, dopamine agonists, and anticonvulsants, often result in side effects and moderate efficacy. RLS disrupts sleep, increases daytime fatigue, and thereby affects quality of life; many patients turn to integrative medicine for answers.

In this review article, Bega and Malkani summarize and analyze clinical trials involving non-conventional treatments for RLS. Reliable data support the following:

1. *Increase physical activity to address RLS symptoms.* The type and duration of activity and mechanism of action all need further study. Aerobic exercise with resistance training focused on lower limbs seems the most promising intervention in this category.

2. *Supplement with oral iron for patients with RLS who have low serum ferritin levels (< 40-50 ng/mL) with or without anemia.* Additional studies are needed to identify iron formulations and optimal duration of treatment. Oral iron supplements (typically 325 mg ferrous sulfate BID with vitamin C) can cause constipation; more concerning is the risk of anaphylaxis with infused iron. Dietary intervention to increase serum ferritin levels is not well studied in the treatment of RLS.

3. *Consider supplementation with vitamins E, C, and D.* Data are unclear if levels should be checked routinely in RLS. One study compared 400 mg vitamin E, 200 mg vitamin C, and a combination of the two with placebo in hemodialysis patients with RLS. Although results look impressive for each intervention arm, short duration of the study and limited participants limit conclusive recommendations.

Preliminary but non-conclusive studies on the following interventions warrant further investigation: yoga, acupuncture, compression devices, light therapy, cognitive therapy, valerian, and Chinese herbs.

CONCLUSION

Well-designed, robust, randomized, controlled trials are needed to better understand the role of alternative treatments and integrative techniques in caring for patients with RLS. The interventions currently supported by sufficient numbers of valid medical studies are physical activity (especially aerobic exercise with lower limb resistance training) and supplemental iron when serum iron is low. Several other interventions show promise; future studies should clarify the role of these non-pharmaceuticals in treatment of RLS. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:

1. Read and study the activity, using the references for further research.

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CME QUESTIONS

1. Which of the following is true regarding a low-sodium diet?
a. It is protective of cardiovascular disease, but only in people with hypertension.
b. It may lead to increased cardiovascular events in people with or without hypertension.
c. It causes increased all-cause mortality only in normotensive individuals.
d. It has no connection to estimated urine sodium excretion.

2.. The combination of pravastatin plus vitamin D:
a. is associated with unacceptable muscle pain in most people.
b. is biologically implausible for the prevention of migraine.
c. is effective in the prevention of headaches in adults with episodic migraine.
d. has been proven to eliminate the need for all other migraine prevention agents.

3. An 8-year-old patient with autism spectrum disorder presents with parents requesting safe, evidence-based recommendations to assist with symptoms of agitation in the classroom. According to Klein and Kemper, appropriate recommendations include which of the following?
a. Active, healthy lifestyle and restrictive diet
b. Restrictive diet and occupational therapy
c. Active, healthy lifestyle and applied behavioral analysis
d. Active, healthy lifestyle and acupuncture combined with psychopharmacology (risperidone or aripirazole)

4. Which of the following statements is true regarding restless legs syndrome (RLS)?
a. RLS typically occurs when a person is overactive and fatigued; often symptoms are relieved by rest.
b. Medical evidence supports the use of iron supplements in RLS only when a patient has low serum iron levels (< 40-50 ng/mL) with or without anemia.
c. RLS, while unpleasant, does not typically interfere with daytime functioning.
d. Medical evidence supports the use of exercise, lower limb resistance training, and iron supplementation in patients with RLS regardless of serum iron level.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- present evidence-based clinical analyses of commonly used alternative therapies;
- make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
- describe and critique the objectives, methods, results, and conclusions of useful, current, peer-reviewed, clinical studies in alternative medicine as published in the scientific literature.

[IN FUTURE ISSUES]

Seafood consumption and brain mercury level

Health benefits of cocoa flavonols

Complementary therapies for preoperative anxiety

Healthy diet, gut microbiome, and insulin sensitivity