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HYPERTENSION

ABSTRACT & COMMENTARY

Blood Pressure Control: Exercise vs. Meds

By Eric Neilson, MD, and Nancy Selfridge, MD

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Dr. Neilson and Dr. Selfridge report no financial relationships relevant to this field of study.

SYNOPSIS: A random-effects network meta-analysis demonstrated comparable reductions in systolic blood pressure among normotensive and hypertensive participants using either antihypertensive medication or exercise interventions.

SOURCE: Naci H, Salcher-Konrad M, Dias S, et al. How does exercise treatment compare with antihypertensive medications? A network meta-analysis of 391 randomized controlled trials assessing exercise and medication effects on systolic blood pressure. *Br J Sports Med* 2019;53:859-869.

Hypertension is one of the most common causes of morbidity and mortality in the world. It is also modifiable. The 2017 American College of Cardiology and the American Heart Association guidelines have expanded the categories of hypertension to now include people at risk of developing the disease and its associated complications, and recommend lifestyle modification, including exercise programs, as a key component in the treatment of each of these categories.[1]

In this network meta-analysis, Naci et al showed that the large amount of data available regarding systolic blood pressure (SBP)-lowering effects of antihypertensive medications are quite consistent. Although research evidence on the effect of exercise is more limited and variable, it too can be as effective at reducing SBP, especially in patients with hypertension.

Naci et al analyzed pooled data from recently published meta-analyses and randomized, controlled trials (RCTs) of exercise or antihypertensive medication effects on SBP. Exercise intervention trials included endurance, dynamic resistance, isometric resistance, or combinations of endurance and dynamic resistance lasting at least four

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Summary Points

- The greatest benefit was seen among hypertensive participants with a systolic blood pressure (SBP) ≥ 140 mmHg using a combination endurance and dynamic resistance program, with a reduction of 13.51 mmHg in mean SBP.
- The medication effects depended on the dose and medication class, and the exercise program impacts depended on the program type and intensity.
- Major areas of future consideration are direct comparison studies of medication vs. exercise and standardized exercise studies with larger sample sizes that include variations in gender and ethnicity.

weeks. Medication intervention eligibility was based on the British National Formulary dosing criteria and included studies of angiotensin-converting enzyme inhibitors (ACE-I), angiotensin-2 receptor blockers (ARB), β-blockers, calcium channel blockers (CCB), or diuretics. Mean SBP changes with a 95% confidence interval were calculated for each treatment modality, and comparison data were compiled.

Results are summarized in Table 1. (*Note: Values were omitted in the publication for β-blockers, although the mean and 95% confidence interval were shown in a comparison graph*.) Overall, both exercise and medication interventions lowered SBP. When comparing different types of exercises, endurance, isometric resistance, and a combination showed the greatest improvements in SBP. Variations in intensity did not demonstrate statistically significant differences. The largest medication decreases in SBP were from CCB classes. Among patients with hypertension, reductions were greatest in the combination exercises group and outperformed the largest medication reductions by an average of 1-3 mmHg.

Limitations of the review, affecting its internal validity, primarily reflected limitations in the original studies. These included significant heterogeneity within the exercise studies, limitations in reporting, and methodological flaws (e.g., small sample sizes, lack of blinding of investigators and participants in exercise trials, blood pressure change as a secondary or tertiary outcome for many of the exercise studies).

Upon conclusion of the analysis, the authors noted the need for more robust research consisting of larger-scaled, well-designed studies comparing the effectiveness of antihypertensive medication directly to various types and intensities of exercise in reducing blood pressure in hypertensive patients. Additional investigations into types and timing of monitoring methodologies for more rigorously structured exercise programs and for measured outcomes are critical to the study of exercise and its influence on disease prevention and treatment.

■ COMMENTARY

Additional evidence supports the contribution that exercise makes to living a healthy life, in this study, by decreasing SBP.[2-4] A blood pressure of 120-129/> 80 mmHg now is considered elevated, and clinical guidelines recommend nonpharmacological lifestyle interventions, including exercise.[1] A sedentary lifestyle, in and of itself, is a risk for cardiovascular disease, and exercise has demonstrated broad benefits for cardiovascular health.[5] However, the benefits of exercise do not just stop at the heart. Exercise is important for the growth and development of children, reducing the incidence and impact of diseases such as diabetes and cancer, improving mental health, and lowering the risk of falls and their related injuries in older populations.[4]

The challenge is how to help and influence people to initiate and maintain a regular beneficial exercise regimen. Fewer than 30% of people adhere to current exercise recommendations, and the numbers are even worse for women and adolescents (19% and 20%, respectively). This fact is costing people their lives, an estimated 10% early mortality, and more than an estimated $110 billion in healthcare expenditures.[4] Adhering to recommendations of moderate-intensity exercise for 150 minutes per week with additional

Table 1: Summary of Exercise and Medication Effects on Baseline SBP in All Groups and SBP ≥ 140 mmHg Groups		
	All Groups	**SBP ≥ 140 mmHg**
All exercise interventions	-4.84 (-5.55 to 4.13)	-8.96 (-10.27 to -7.64)
All medications		-8.80 (-9.58 to -8.02)
Endurance	-4.88 (-5.96 to -4.06)	-8.69 (-10.13 to -7.25)
Resistance	-3.50 (-4.91 to -2.09)	-7.23 (-10.58 to -3.87)
Isometric	-5.65 (-8.21 to -3.13)	-4.92 (-10.28 to 0.38)
Combination exercise	-6.49 (-8.17 to -4.82)	-13.51 (-16.55 to -10.45)
ACE-I		-7.33 (-8.75 to -5.91)
ARB		-8.14 (-9.62 to -6.69)
Beta-blocker		Values omitted from publication
CCB		-10.58 (-12.03 to -9.14)
Diuretic		-8.06 (9.48 to -6.64)
Low-intensity exercise	-4.60 (-6.51 to -2.69)	
Moderate-intensity exercise	-5.41 (-6.37 to -4.46)	
High-intensity exercise	-3.87 (-5.11 to -2.65)	
Low-dose medication		-8.29 (-9.13 to -7.46)
High-dose medication		-10.71 (-11.94 to -9.46)

Values are means (95% confidence interval)
ACE-I: angiotensin-converting enzyme inhibitors; ARB: angiotensin-2 receptor blockers; CCB: calcium channel blockers

muscle-strengthening exercises two days a week is critical to reversing these trends.[4]

Physicians are encouraged to play a role in counseling patients to exercise more often. There is some evidence that this support translates into a more active lifestyle for many.[4,6] Training medical students and encouraging practicing physicians to promote exercise consistently as an evidence-based intervention may help move us closer to a tipping point in terms of patient adherence to exercise recommendations.[6] When exercise interventions are added to other nonpharmacological interventions, such as weight loss, an evidence-based heart-healthy DASH diet, and reductions in sodium intake, even larger reductions in SBP are observed.[1] Naci et al are to be applauded for their contribution to this end. ■

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HERBAL THERAPY

ABSTRACT & COMMENTARY

Oral Capsaicin for Muscle Energy

By David Kiefer, MD, Editor

SYNOPSIS: Ten men ran 1,500 meters six seconds faster and were slightly less fatigued after ingesting 12 mg of capsaicin than after ingesting a placebo capsule.

SOURCE: de Freitas MC, Cholewa JM, Gobbo LA, et al. Acute capsaicin supplementation improves 1,500-m running time-trial performance and rate of perceived exertion in physically active adults. *J Strength Cond Res* 2018;32:572-577.

Well into the summer exercise and event season, patients may ask their healthcare providers what would provide that extra "boost," that nudge toward greater endurance or strength, and better times running, cycling, or swimming. Assuming optimal nutrition, sleep, and aerobic training, active adults may consider any number of supplements for sports or exercise enhancement.[1] One familiar example is creatine,[2] but there are many others.[1]

To expand on the clinical evidence for the use of supplements to affect exercise physiology, de Freitas et al chose a specific "middle distance" activity, the 1,500-meter run. Rather than a sprint or marathon, the 1,500-meter run is most limited by muscle fatigue as mediated by several physiological parameters that affect muscle force. (*See Table 1.*)

Into this milieu, the authors of a series of animal and human clinical trials found benefits for the use of capsaicin. Capsaicin is a compound found in species of cayenne pepper (*Capsicum* spp., Family Solanaceae) or chili pepper.[3] There are some data for its analgesic use topically,[4] but it also may shift muscle physiology when used orally. The authors cited mixed results from clinical trials that included humans doing exercise. Their own work found benefits with 12 mg of isolated capsaicin, whereas other groups using cayenne pepper powder (3 g, providing 28 g of capsaicin) were not able to show improvements in athletes' performance. Clearly, more data were needed.

de Freitas et al conducted this randomized, double-blind study in 10 men (average age 23.5 years) in Brazil who were not regular runners in the previous six months, were not taking any performance-enhancing substance, and did not have any heart or musculoskeletal contraindication to participation. They were instructed to not change their diet or add supplements to their daily regimen.

There were three visits. During visit 1, researchers measured height, weight, and bioimpedance. One week later, during visit 2, participants completed a 24-hour dietary recall and were randomized to either a placebo capsule (50 g of starch) or capsaicin (12 mg) 45 minutes before the 1,500-meter run, which was done on an outdoor 400-meter track as fast as the participants could. After the run, each participant completed a survey instrument called the Rate of Perceived Exertion (a scale from 6-20) and had blood analyzed for lactate. Seven days later, for visit 3, each participant repeated the dietary recall and the 1,500-meter run, ingesting the alternate intervention (placebo or capsaicin), to complete the crossover analysis.

With respect to results, there was no difference in nutrition as per visit 2 and visit 3; presumably, major shifts in the diet before the time trials could have affected the primary outcomes of this study. With respect to running times, the placebo group time was listed as 376.7 seconds, whereas the capsaicin group came in at 371.6 seconds ($P = 0.009$). Of note, the times in both arms were quite fast, between six- and seven-minute miles. In addition, the Rate of Perceived Exertion in the placebo group was 18.8 vs. 18.0 in the capsaicin group ($P = 0.022$). Furthermore, in each arm of the trial, there was a predictable rise in blood lactate after exercise, which decreased over time; there was no difference in this change between the groups. There was no comment on side effects or other adverse events.

Summary Points

- This was a double-blind, randomized, controlled trial in 10 men to study the effects of one dose of capsaicin (12 mg capsule) 45 minutes before a 1,500-meter run.
- Slight, but statistically significant, improvements in running time and rates of perceived exertion were documented when compared to the placebo arm.
- There was no difference in lactate levels between the capsaicin and placebo arms, commenting on potential mechanisms of action.

Table 1: Factors That Might Decrease Muscle Force in Middle-Distance Aerobic Activities

- Creatine phosphate availability decreases
- Accumulation of hydrogen ions
- Accumulation of inorganic phosphate
- Accumulation of reactive oxygen species
- Acidosis occurs
- Decreased release of calcium by the sarcoplasmic reticulum

■ COMMENTARY

Exercise physiology, as with all other aspects of our physiology, is complex. Many variables are involved in promoting the optimal function of muscles in coordination with the cardiovascular and pulmonary systems. These researchers used a small trial to show small benefits on running time and perceived exertion for a 1,500-meter run with capsaicin supplementation. The statistical significance may override clinical significance in this case; these runners were fast and they gained six seconds over the course of about a mile. We may be hard pressed to

find applicability for this intervention to a standard clinical practice. Furthermore, we are missing commentary of tolerability and safety of the intervention. The authors commented on gastrointestinal limitations to capsaicin doses greater than 30 mg, and there are certainly some people who have an increase in gastroesophageal reflux disease with spicy foods, including cayenne pepper. We should keep in mind that this intervention may not work for everyone.

It is possible that oral capsaicin does nudge the physiology in significant ways. The authors cited prior research that capsaicin is an agonist of the TRPV1 receptor; this receptor may activate the sympathetic nervous system and foster improved energy utilization that could enhance exercise performance, as well as lead to analgesia, another benefit when facing the rigors of physical activity. The lack of change in blood lactate between capsaicin and placebo arms negates some potential mechanisms of action, such as muscle glycogen preservation during activity.

This is a specialized use of a plant extract, one unlikely to be replicated through culinary means. Not only is it unreasonable to think about eating a spicy, chili pepper-laden meal right before a mile run, but the content of capsaicin in chili peppers is variable.[5] There probably is no substitute for healthy nutrition, regular training, and adequate rest to promote exercise performance, although the results of this small clinical trial point to perhaps interesting future research for substances that may have physiological effects. ■

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MENTAL HEALTH

ABSTRACT & COMMENTARY

Digital Applications Used in Mental Health Treatment: Two Randomized Studies

By Ellen Feldman, MD

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

SYNOPSIS: Researchers found an improvement in socialization in children with autism and a decrease in acrophobic (fear of heights) symptoms in adults in two distinct studies using different forms of virtual reality and digital applications.

SOURCES: Voss C, Schwartz J, Daniels J, et al. Effect of wearable digital intervention for improving socialization in children with autism spectrum disorder: A randomized clinical trial. *JAMA Pediatr* 2019; Mar. 25. doi: 10.1001/jamapediatrics.2019.0285. [Epub ahead of print].

Donker T, Cornelisz I, van Klaveren C, et al. Effectiveness of self-guided app-based virtual reality cognitive behavior therapy for acrophobia: A randomized clinical trial. *JAMA Psychiatry* 2019; Mar. 20. doi: 10.1001/jamapsychiatry.2019.0219. [Epub ahead of print].

"Most people with mental illness are not treated," concluded a researcher looking at data from a 2007 landmark study published in *The Lancet*.[1] Despite advances in treatment of mental illness since this study, financial concerns, lack of providers, and perceived stigma remain strong barriers to appropriate and timely mental health intervention.[2,3]

It is no wonder that efforts to provide cost-efficient, easily accessible, and stigma-free mental health care are rising. As internet access has spread, interest in providing this care via digital delivery has heightened. Reflecting the popularity of online solutions, numerous lay and medical publications have started publishing lists of "best mental health apps."[4-6] Yet, rigorous studies evaluating the effectiveness of apps in a controlled fashion are lacking.

Two pioneering studies counter this trend. Both published in *JAMA*, the authors of these two disparate studies evaluated mental health care digital delivery via different forms of virtual reality. The first was a randomized, controlled study of 71 California children with autism, and the second was a randomized, controlled study of 193 Dutch adults with acrophobia. These studies involved distinct disorders and participants; the link between the studies is that both are among the first

controlled investigations of the effect of digital apps in the treatment of mental illness.

The prevalence of autism spectrum disorder (ASD) is rising. Affecting one in 59 U.S. children and approximately 2-3% of the adult population, this neurodevelopmental disorder is a lifelong condition, often identified in early childhood and typically before a child reaches school age. ASD presents with a cluster of symptoms across a range or spectrum of severity. Core symptoms of this disorder include difficulty attaining age-normalized social skills (i.e., maintaining eye contact), interpreting facial expressions accurately, and understanding nuances of conversation. These skill deficits often lead to functional impairment and unwanted behaviors, including aggression and self-harm.[7,8]

ASD medications are limited to symptom relief and targeted to specific behaviors. Socialization rarely can be addressed with psychotropic agents. Applied Behavior Analysis (ABA) is a specialized type of behavioral therapy that has evidence of efficacy in this realm. Unfortunately, the expense, time commitment (20 hours weekly over a two-year span), and shortage of qualified therapists make attaining ABA unrealistic for many young patients.[7,8]

Voss et al looked at enhancing gains made with ABA by adding on a digital intervention dubbed Superpower Glass (SG) by the children who first piloted the device. Seventy-one children between the ages of 6 and 12 years who were diagnosed with ASD and lived within driving distance of Stanford University were sorted randomly into two groups: treatment as usual plus intervention and treatment as usual. To qualify, the children needed to be receiving ABA therapy at least twice weekly.

The SG "smart vision" system runs via Google Glass (worn by the child) and a connected smartphone app, which provides real-time audio and visual information to the wearer of the glasses regarding facial expressions, engagement, and recognition of emotion. Each family in the intervention arm was instructed to have participants wear the glasses and perform specific social recognition tasks (as set by the app) four times weekly for 20 minutes over six weeks. A family member managed the connected app for most sessions, but this was tasked to the ABA therapist at least once a week.

Of the 71 children beginning the study, 52 remained at study termination. More than half of the families of the 13 dropouts from the intervention arm explained that the device was not suitable for the child ("too challenging"). The remining six dropouts were from the control arm. One family reported the child wearing the glasses had an adverse effect.

At the six-week study conclusion, improvement was measured with several validated scales looking at various aspects of socialization. Although all scales demonstrated improvement and all results were assessed using an intention-to-treat analysis, the only scale showing statistical significance of improvement was the Vineland Adaptive Behavior Scale (VABS-2). This scale measures several skills, including communication and adaptive behaviors.[9] At the initial six-week mark, a mean treatment impact of 4.58 points ($P = 0.005$) was measured for the intervention group.

However, at the six-week follow-up, mean improvement on the VABS-2 declined in the SG group and was no longer statistically significant.

The Voss et al study raises several questions regarding home digital delivery of an intervention for mental health. It is encouraging that initial results demonstrated significant impact. However, the loss of effectiveness over time is essential to understand before drawing firm conclusions and may point to a need for a longer treatment course, a practice period, or other factors.

It also is important to understand that ASD occurs on a spectrum. Inclusion criteria in this study did not account or match for disease severity, and the relatively large dropout rate may be reflective of this heterogeneity. On the other hand, the relatively homogenous geographic selection criteria raises other limitations to generalizability of results. Finally, the authors did not control for the additional time parents were spending with the

Summary Points

- The authors of two different studies investigated the use of digital applications (apps) for the delivery of mental health interventions.
- Study 1 was a randomized, controlled trial of 71 children with a diagnosis of autism. A Google Glass with specialized software, wirelessly connected to a smartphone app, provided video and audio cues regarding facial expression. Participants wearing the glasses and performing specific tasks had significant improvement in a socialization scale after six weeks.
- Study 2 was a randomized, controlled study involving 193 adults with acrophobia. Participants were given access to an app delivering virtual reality, cognitive-based therapy via cardboard, low-cost virtual reality goggles. At three months, the intervention group showed significant acrophobia symptom reduction.

intervention participants, making it difficult to know if any outcomes were due to this interaction with or without the SG.

Even with these limitations, the study results showed the potential for addressing difficult-to-treat symptoms with a relatively low-cost, easily accessible, home digital intervention for appropriate patients with ASD.

In the second study, Donker et al noted that specific phobias are more common than many providers may realize. With a lifetime prevalence of 16.6 among U.S. adults, this group of disorders holds the dubious honor of ranking among the most common mental health disorder in this population — second only to depression.[10]

According to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), specific phobias have seven diagnostic criteria. In general, diagnosis requires functional impairment due to significant fear or anxiety about a specific situation out of proportion to actual danger. Without adequate treatment, these disorders may worsen and lead to depression and generalized anxiety. Evidence-based treatment largely supports the use of cognitive-behavioral therapy (CBT) with progressive exposure to the situation or feared stimulus. Some studies suggest that virtual exposure to the stimuli may be effective as well.[10-12]

Acrophobia, the most common of all specific phobias, is a specific phobia regarding fear of heights.[13] In this Dutch study, participants from the general population were recruited via advertising. Eligibility criteria included attaining a score above a set cutoff on the Acrophobic Questionnaire-Anxiety (AQ), falling into the 18- to 65-year-old age range; and having access to an Android device with a gyroscope. Prospective participants with severe depression and/or psychotropic medication were not eligible for inclusion in this study.

After randomizing the 193 eligible participants into an intervention and wait list group, the intervention group received access to ZeroPhobia, an Android app providing a self-paced virtual reality (VR) CBT program. In addition, participants were asked to purchase cardboard VR goggles ($10).

The CBT program was designed to be completed over three weeks and was broken into six segments ranging from 5 to 40 minutes. The VR exposure, an immersive experience navigable via gaze, was introduced in the third segment. Practice sessions were encouraged throughout the entire period.

The primary outcome was score on the AQ (the same questionnaire used to determine eligibility) and measured at baseline, three weeks, and at the three-month follow-up. Secondary outcomes, including a depression inventory and a measure of user friendliness of the intervention, also were completed online. Researchers blinded to the intervention interpreted all scores, and all results were subjected to an intention-to-treat analysis.

Results at post-test and at three months showed a significant reduction in AQ scores among the intervention group, with a mean score reduction of 40 points ($P < 0.001$) and a significantly large effect size as indicated by Cohen d = 1.14 (95% confidence interval, 0.84-1.44.) The effect size increased to d = 2.68 when comparing baseline and three-month follow-up scores within the intervention group only.

The secondary measures showed no change in the depression inventory symptoms and a general rating of "user-friendly" for the app. There were no deleterious side effects reported, but 24 respondents noted at least transient symptoms of cyber sickness, or nausea and dizziness when using the VR exposure. Notably, there was a correlation between experience of cyber sickness and intensity of response.

As there appeared to be significant benefit at the post-test mark, all wait-list control participants were given access to the app at that time. Thus, the three-month follow-up statistics did not include a comparison to control, but showed an extension of previously noted gains in specified measures as indicated by the substantial increase in effect size noted above.

Notably, one of the study limitations was a large pre-treatment attrition rate of 22% in the intervention group because of incompatibility of the app with the participant device. Other limitations included a homogenous sample, data reliance on self-reported app use and self-reported scoring, and the relatively limited follow-up period.

Overall, the robust results are encouraging and show that VR CBT delivered via a digital app may be a useful tool in the fight against acrophobia.

When considering the two studies as a whole, it is clear that although both showed promise, the results are preliminary and are unable to be generalized until further research and well-designed studies are completed. However, the significance of both lie in the process of subjecting newer techniques in mental health care to the time-tested process of rigorous scientific validation. The beauty of many online therapeutic interventions is easy accessibility, but this access becomes a double-edged sword when the validation process is missing.

Our job as providers includes helping patients sort through a plethora of medical information and direct them toward accurate and useful facts to aid in wellness and treatment. Patients with mental health disorders often are in a vulnerable state. Studies with

scientifically backed data can elevate a treatment discussion and remind all involved of the need to have sufficient information when beginning the process of weighing potential risks and benefits for a particular intervention. ■

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CANCER

ABSTRACT & COMMENTARY

Hot Beverages and Esophageal Cancer

By David Kiefer, MD, Editor

SYNOPSIS: In a cohort of more than 50,000 people, there was an increased risk of esophageal squamous cell carcinoma in those who consumed higher quantities of mostly black tea at higher temperatures.

SOURCE: Islami F, Poustchi H, Pourshams A, et al. A prospective study of tea drinking temperature and risk of esophageal squamous cell carcinoma. *Int J Cancer* 2019; Mar 20. doi: 10.1002/ijc.32220. [Epub ahead of print].

For many of us, warm beverage consumption is an important routine to start our day or stave off the chilling effects of those long winter days. And, the drinking of teas (infusions) and coffee is pan-cultural; rare is the locale lacking in medicinal or culinary hot drinks. With this context, an article title that dampens our enthusiasm for this ritual is eye-catching. The authors of this population-based study in Iran attempted to explore some of the concerns, as cited in their introduction, with regularly exposing our bodies to hot liquids. The research studies on this topic have shown a mixture of results, some connections to esophageal cancer, some without an obvious cause-effect, possibly, as the authors hypothesized, due to flaws in data connection, such as recall bias of the study participants regarding their memory of the temperature of the beverages consumed in the past. These uncertainties have led to some ratings of "very hot" (≥ 150° F) beverage drinking as being "probably carcinogenic," rather than the more worrisome "carcinogenic."

This prospective study occurred in one province in Iran, a geographic region with a particularly high rate of esophageal squamous cell carcinoma (ESCC), which previous studies had associated with tea drinking. The authors followed 50,045 adults between the ages of 40 and 75 years through home interviews or telephone calls. Research staff conducted interviews to identify ESCC risk factors and collected data about demographics and nutrition.

Summary Points

- This was a 10-year prospective cohort study that included more than 50,000 adults in Iran.
- Tea, primary black tea, consumption was analyzed, focusing on the temperature and quantity of tea consumed and the connection to risk of squamous cell carcinoma (SCC) of the esophagus.
- The risk of esophageal SCC was greatest in people consuming 700+ milliliters of tea daily, but, more specifically, tea that was > 60° C.

Table 1: Hazard Ratios for Esophageal Squamous Cell Carcinoma Risk for Tea Temperatures, Both Measured and Subjectively Estimated	
Variable	**Hazard ratio (95% confidence interval)**
≥ 60° C (compared to < 60° C)	1.41 (1.10-1.81)
Self-perceived "very hot" tea (compared to cold or lukewarm)	2.41 (1.27-4.56)
Less than five minutes from pouring to drinking	1.10 (1.01-1.21)
Higher consumption of black, green, and green and black tea	Variable HR (details in research study's Table 1)

With respect to tea drinking, the research assistants asked study participants for a subjective analysis of how warm or hot the tea they drink usually is, as well as the time between the tea pouring and drinking. In addition, participants were given tea the temperature of which was measured, and they were asked how the tea they normally drink compares to that tea.

Attempts were made to contact participants annually; less than 1% have been lost to follow-up. On average, participants were followed for 10.1 years, during which records indicated that 328 cases of esophageal cancer occurred. Of these 328 cases, 11 were adenocarcinoma by pathology; 317 were presumed to be SCC (285 by pathology, 32 considered "likely" cases). Statistics were run on these ESCC cases in the cohort of 50,027 people, and compared to black tea consumption in mL per day (in quintiles) and tea temperature ranges of < 60° C, 60-64° C, and ≥ 65° C. Green tea consumption was low (average 42 mL daily) compared to black tea (> 1,100 mL daily). Drinkers were split into two groups based on the quantity consumed. The hazard ratios for various tea temperatures are shown in Table 1.

The researchers then ran the numbers for tea temperature and tea amount. For drinkers of tea (black plus green) < 60° C, it did not matter how much tea they drank; there was no increased ESCC risk. For drinkers of tea ≥ 60° C, higher amounts showed an increased risk as per Table 2.

Table 2: Hazard Ratio for the Consumption of Black and Green Tea ≥ 60° C	
Daily tea quantity consumed (mL)	**Hazard ratio (95% confidence interval)**
1-699	1.10 (0.61-2.00)
700-1,299	1.95 (1.17-3.25)
1,300+	1.87 (1.13-3.11)

■ COMMENTARY

In this prospective cohort study that included more than 50,000 people followed over 10 years, Islami et al found that the risk of ESCC was higher for people who drank more beverages that were hot (rather than warm). They pointed to the improvements in their research methodology over past work, namely that an effort was made, through several techniques, to quantify the temperature and amount of the tea consumed in a region of Iran particularly known for both its tea drinking and its incidence of ESCC.

In some respects, the connection between hot beverages and cancer makes sense. The researchers documented the carcinogenic potential that can arise from thermal damage to esophageal tissue or from the formation of carcinogenic compounds. In addition, they described why this might occur only past a certain temperature threshold, perhaps due to damage to the esophageal cells that then permit toxins to lead to DNA damage and oncological change. One class of toxins known to affect people in this area are the polycyclic aromatic hydrocarbons (PAHs), which enter the human body through diet or cigarette smoking.

Should we counsel our patients to shy away from that favorite tea or coffee? As with other attempts to extrapolate research on one population to other regions or demographics, it is unclear. The most concerning findings here are in those people who drank both a lot of tea and at a high temperature. And, this was mostly black tea. It would probably be safe to say that if a clinician has patients who fall into those categories, that they would mitigate some of their ESCC risk by moderating both quantity and temperature of the tea consumed. And, Islami et al did not comment on coffee, nor, for the most part, green tea. The commentary from the authors on the possible involvement of toxins, too, is an interesting bent to these results. It makes one branch out from the temperature and quantity of warm/hot beverages to consider plant quality (contaminant-free sources, for instance), in case the carcinogenic transformation involves toxins, too. ■

ABSTRACT & COMMENTARY

Behavioral Interventions for Menopausal-Related Insomnia Improve Depression

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

SYNOPSIS: In a randomized, controlled trial comparing the behavioral interventions cognitive behavioral therapy for insomnia (CBTI) and sleep reduction therapy (SRT) to a control intervention of sleep hygiene education, investigators found CBTI and SRT therapy improved insomnia and depressive symptoms in postmenopausal women with menopausal-related insomnia.

SOURCE: Kalmbach DA, Cheng P, Arnedt JT, et al. Treating insomnia improves depression, maladaptive thinking, and hyperarousal in postmenopausal women: Comparing cognitive-behavioral therapy for insomnia (CBTI), sleep restriction therapy, and sleep hygiene education. *Sleep Med* 2019;55:124-134.

Insomnia symptoms are common complaints during the menopausal transition, and up to 50% of women experience these symptoms.[1] Menopausal-related insomnia disorder describes insomnia that occurs or is exacerbated during perimenopause or menopause, and is believed to be related to fluctuations in estrogen, progesterone, and cortisol levels. Effective treatments include cognitive behavioral therapy for insomnia (CBTI), sleep reduction therapy (SRT), hormone replacement therapy (HRT), antidepressants, exercise, and yoga.[2] Insomnia also is strongly correlated with depressive symptoms in adults. In addition, depressive symptoms are increased during the menopausal transition. Kalmbach et al attempted to address the effect of CBTI or SRT on insomnia and depressive symptoms in women with menopausal-related insomnia.

Summary Points

- This was a randomized study of 117 postmenopausal women with insomnia, studying the effects of sleep hygiene education, sleep reduction therapy (SRT), or cognitive behavioral therapy for insomnia (CBTI).
- Over the course of the six-week study, SRT and CBTI improved both depression and insomnia; sleep hygiene education did not lead to any significant changes.

Behavioral interventions often are considered first-line interventions for insomnia in the general adult population.[3] Common behavioral interventions for insomnia include CBTI and SRT. The theory behind the effectiveness of these treatments is that acute insomnia can progress into chronic insomnia because of cognitive arousal (rumination and worry) and dysfunctional beliefs about sleep (catastrophizing negative effects of a poor night's sleep). CBTI treatments aim to address this component of insomnia comprehensively, while SRT is a unique intervention that is part of the full CBTI protocol that specifically addresses time in bed (TIB).

SRT is a standard behavioral strategy used as part of CBTI and as a standalone intervention. It involves restricting a patient's TIB (sleep window) to match his or her average self-reported total sleep duration. The sleep window is titrated weekly, based on sleep efficiency (the proportion of TIB spent asleep), to identify the patient's core sleep requirement. Spielman et al proposed that decreasing a person's opportunity to sleep across successive nights would build homeostatic sleep pressure, stabilize circadian control of sleep and wakefulness, and dampen presleep cognitive and physiological hyperarousal, which would lead to less time to fall asleep and more consolidated, uninterrupted sleep.[4]

Kalmbach et al used a single-site, randomized, controlled trial format to randomize 117 postmenopausal women (56.34 ± 5.41 years of age) with peri- or postmenopausal onset of insomnia to one of three treatments: sleep hygiene education, SRT, or CBTI. Exclusion criteria included sleep apnea, restless legs, bipolar disorder, and prior CBTI. Blinded assessments were performed at baseline, post-treatment (approximately six weeks), and six-month follow-up. The authors used the Beck depression inventory, second edition (BDI-II) to measure depression and a variety of scales to assess cognitive and behavioral properties associated with insomnia: dysfunctional

beliefs and attitudes about sleep scale (DBAS), presleep arousal scale (PSAS), event-related rumination inventory (ERRI), and Penn State worry questionnaire (PSWQ). Of the study participants, 3.4% were on HRT and 23.1% underwent medical menopause. Vasomotor or other menopausal symptoms were not elicited and, thus, not used in randomization. In addition, 4.3% of participants endorsed moderately severe depression at intake (BDI-II > 20) while the average BDI-II was 8.26 ± 5.00 (subclinical depression range). All interventions were offered in a primary care or sleep medicine office-based setting over six weeks in either face-to-face, telephone, or email format.

Improvements in insomnia were strongly correlated with improvements in depression and dysfunctional beliefs about sleep in both post-treatment and six-month follow-up. Patients receiving SRT or CBTI both reported lower depressive symptoms six months after completing treatment. SRT patients reported a medium decrease in depressive symptoms, whereas CBTI patients reported a larger decrease in symptoms. Change from pre- to six-month follow-up BDI-II score was -2.91 ($P < 0.01$) in the SRT group and -5.14 ($P < 0.001$) in the CBTI group. Sleep hygiene education alone did not produce any durable treatment effects. In fact, depressive symptoms were higher at the six-month follow-up. SRT direct effects on depression were not captured until the six-month follow-up visit. Results showed that compared to sleep hygiene education, short-term specialized behavioral interventions (CBTI and SRT) helped alleviate subclinical depressive symptoms and improve insomnia by reducing maladaptive thinking and somatic hyperarousal.

■ COMMENTARY

A paucity of data exists regarding behavioral interventions specifically for insomnia related to menopause, despite its high prevalence in this population. Kalmbach et al described an effective model for a two- to six-session office-based behavioral intervention, which was delivered by a registered nurse under guidance of a licensed mental health professional. Access to evidence-based behavioral interventions for insomnia has been a barrier to treatment in many clinical settings. This intervention could be provided in ambulatory settings for the common complaints of menopausal-related insomnia and depressive symptoms.

This reflects the trend of delivering behavioral insomnia interventions in an integrated medical care setting. The Veterans Administration (VA), which also sees a high prevalence of insomnia in its population, but struggles with access, has released an evidence-based online app, the CBT-i Coach. This free, publicly available, patient-facing smartphone app is intended to augment clinician-delivered CBTI by facilitating the delivery of major CBTI treatment components, including sleep educational materials, daily sleep diary completion, stimulus control guidelines, SRT, anxiety management, and cognitive therapy tools.[5] It is not specific to the VA population and can be used for general insomnia by anyone.

Studying specific behavioral interventions for insomnia in this population can help identify the most effective interventions for menopausal-related insomnia. Kalmbach et al found that CBTI was most effective, followed by SRT. Sleep hygiene education had no lasting clinical effect on insomnia or depressive symptoms. They did not address which perimenopausal and postmenopausal patients may respond best to this treatment. This population had a high incidence of medically induced menopause. Vasomotor symptomatology, which is correlated with both insomnia and depression, was not elicited. Furthermore, the women in this study had average BDI scores of 8.26 ± 5.00 and were in the subclinical depression range. It is unclear and not yet recommended for insomnia interventions alone to be used to treat those who meet criteria for clinical depression.

[Cognitive behavioral therapy for insomnia and sleep reduction therapy are easy, side effect free, and effective behavioral treatments for patients with these common menopausal symptoms.]

Obviously, one of the benefits of successful office-based behavioral interventions is the low side effect profile, particularly for women who may not be good candidates for hormone therapy or antidepressant treatment. CBTI and SRT are easy, side effect free, and effective behavioral treatments for many patients with these common menopausal symptoms. Hopefully, more innovative models of delivery will be available to the clinician in the future. ■

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CME QUESTIONS

1. **Which of the following exercise interventions resulted in the largest decreases in mean systolic blood pressure?**
   a. Endurance
   b. Isometric resistance
   c. Dynamic resistance
   d. Combination

2. **Which of the following is true regarding the use of oral capsaicin to enhance muscle performance?**
   a. There are unacceptable adverse effects when capsaicin is used orally.
   b. Topical capsaicin improved the Rate of Perceived Exertion.
   c. Taking 12 mg of capsaicin improved running speed vs. placebo
   d. There was no difference between placebo and capsaicin groups with respect to muscle performance.

3. **Which of the following characteristics of tea consumption in Iran is correlated with an increased risk of squamous cell carcinoma of the esophagus?**
   a. Low temperature tea, but in high quantities
   b. High temperature tea, in low quantities
   c. High temperature tea, in anything but low quantities
   d. There is no correlation between tea consumption and cancer

4. **Which of the following best characterizes sleep reduction therapy (SRT) as a behavioral intervention?**
   a. SRT is an easily accessible and available intervention in most office-based settings.
   b. SRT has not shown an effect on rumination, worry, or catastrophizing a poor night's sleep.
   c. Sleep hygiene interventions include SRT.
   d. SRT involves restricting a patient's time in bed to increase consolidated sleep.

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.

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