

COLUMN

Scanning the Global Literature

In each issue of *Global Advances in Health and Medicine*, we will publish summaries of and commentaries on select articles from journals our editors and other contributors to the journal are reading.

CYTISINE VS NICOTINE FOR SMOKING CESSATION

This randomized, pragmatic, open-labeled trial conducted in New Zealand compared cytisine against nicotine replacement therapy in a sample of 1310 adult daily smokers who had called the national quitline for support. Cytisine is a plant-based alkaloid similar to varenicline and acts on the same nicotinic acetylcholine receptors. Four previous systematic reviews have shown that cytisine is more effective than placebo in both short-term and long-term abstinence, almost doubling the chances of quitting at 6 months. Participants in this study were randomly assigned in a 1:1 ratio to receive cytisine for 25 days at no cost or low-cost nicotine-replacement therapy for 8 weeks, and both groups received behavioral support delivered via the quitline. The primary outcome was self-reported continuous abstinence at 1 month. Cytisine proved more effective than nicotine replacement therapy at 1 week, 1 month, 2 months, and 6 months, although the cytisine group had more self-reported and relatively minor adverse events, mostly nausea, vomiting, and sleep disorders. A planned subgroup analysis showed that cytisine was more effective than nicotine replacement therapy for women compared to men at the primary 1 month point. Limitations of the study included the potential for bias based on the open allocation to treatment, the difference in access to and length of the 2 treatments, the use of self-reported measures, and the study population—quitline callers—may be more motivated to quit than other groups of smokers.



Commentary by Martha Brown Menard, PhD, LMT

Despite its limitations, this is an important study documenting the real world effectiveness of a low-cost generic medication for smoking cessation that offers a potential alternative to both nicotine replacement therapy and varenicline. Two previous studies have found lower quit rates for women using nicotine replacement therapy compared to men, making the result that cytisine was more effective for women than men at the 1-month point intriguing. This is a novel finding that needs further replication. Because the use of tobacco products remains a serious public health problem, comparative effectiveness trials examining cytisine, nicotine replacement therapy, and varenicline that include cost are indeed warranted. The authors note that cytisine has been available

both with and without prescription since the 1960s, mostly in Eastern Europe. It will be interesting to see whether future comparative effectiveness trials will be conducted in the United States, making this inexpensive medication more widely available.

REFERENCE

Walker N, Howe C, Glover M, McRobbie H, Barnes J, Nosa V, Parag V, Bassett B, Bullen C. Cytisine versus nicotine for smoking cessation. *N Engl J Med*. 2014;371(25):2353-62.

TIME-RESTRICTED FEEDING DIETS FOR OBESITY AND METABOLIC HEALTH

Projected global increases in obesity and obesity-related metabolic diseases pose significant public health challenges and contribute to the growing costs of healthcare. Lifestyle interventions, including changes in diet and increased exercise, are still preferred first-line therapies to combat obesity and associated metabolic conditions. However, due to poor adherence, sustained weight management and metabolic health utilizing even clinically proven diet programs are limited to a small percentage of people. Time restricted feeding (TRF) strategies, which focus more on diurnal timing of calorie intake vs quantity or nutritional sources of calories, have been purported to positively impact obesity by more efficiently utilizing circadian rhythms of metabolic pathways. Using a murine model and an impressive battery of coordinated experiments, this study tested the impact of various TRF regimens on body weight, metabolic markers of fitness, metabolomics, and gene regulation.

Noteworthy findings include the following. (1) When mice are fed high-fat, high-sucrose diets, limiting feeding time to a 9-hour window compared to *ad libitum* access to the same food over the entire 24-hour period (equal total calories in both groups), this resulted in a 50% reduction in weight gain over 12 weeks. (2) Positive but less dramatic benefits of TRF were observed with longer feeding windows of 12 and 15 hours. (3) Benefits of TRF were preserved during a weekly cycle that allowed for 2-day “weekend bingeing” (5 d TRF/ 2 d *ad libitum*). (4) TRF helped reverse weight gain in mice with preexisting diet-induced obesity. (5) Multiple measures of metabolic fitness (eg, body composition, lipid profiles) and markers of inflammation, gene regulation, and metabolite dynamics were all positively influenced by TRF and collectively contribute to a multisystem mechanistic understanding of observed improvements in weight control.

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Commentary by Peter Wayne, PhD

TRF studies in mice demonstrate dramatic benefits for weight management and multiple markers of metabolic fitness. These provocative findings support the value of large-scale clinical trials evaluating TRF for treating human obesity and dysmetabolism. The observed pleiotropic beneficial effects of TRF on multiple physiological processes also supports an emerging systems biology view of health, and the potential positive impact that lifestyle changes such as diet can have on multiple risk factors.

REFERENCE

Chaix A, Zarrinpar A, Miu P, Panda S. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. *Cell Metab.* 2014;20(6):991-1005.

RANDOMIZED EFFECTIVENESS TRIAL OF A BRIEF COURSE OF ACUPUNCTURE FOR POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) is a highly prevalent and disabling condition. Recent studies in the US military have identified PTSD in up to 17% of personnel after combat deployment and 9% in military primary care settings. Engel et al conducted a trial of 55 service members who met research diagnostic criteria for PTSD. Participants were randomized to usual PTSD care (UPC) and usual care plus eight 60-minute sessions of acupuncture offered twice weekly. Outcomes were assessed at baseline and at 4, 8, and 12 weeks post-randomization. The mean improvement in PTSD severity was significantly greater among those receiving acupuncture compared to those receiving usual care only. The group receiving acupuncture also showed greater improvements in depression, pain, and physical and mental health functioning. Pre-post effect sizes for these outcomes were reported as being large and robust.



Commentary by Mary Jo Kreitzer, PhD, RN, FAAN

Given the prevalence of PTSD in both military and civilian populations, the findings of this study are quite significant clinically and warrant further investigation. It is estimated that fewer than half of people diagnosed with PTSD seek treatment. Acupuncture is a reasonably low-cost intervention that is widely accessible and can be offered in a variety of settings, including primary care offices. While this study was small, the effect sizes for the outcomes were large. A larger trial is warranted to confirm the findings of this study. As noted by the authors, it would also be interesting to study whether acupuncture might hold promise for engaging the large number of people untreated for PTSD who do not seek PTSD treatment due to stigma or lack of confidence in standard modalities.

REFERENCE

Engel CE, Cordova EH, Benedek DM, et al. Randomized effectiveness trial of a brief course of acupuncture for posttraumatic stress disorder. *Med Care.* 2014;52(12 Suppl 5):S57-64.

PREVENTING LOSS OF INDEPENDENCE THROUGH EXERCISE IN OLDER ADULTS WITH DEMENTIA

This paper reports an observational study of 11 individuals with mild to moderate dementia who participated in a 36-week crossover pilot clinical trial of an integrative exercise program which included tai chi, yoga, and dance movement therapy. The written notes of exercise instructors and written summaries prepared by research assistants were analyzed alongside video-recordings of program classes. The analyses suggest the program may lead to potential changes for participants with mild to moderate dementia. Specifically, functional changes such as increased body awareness and movement memory; emotional changes including greater acceptance of resting and developing a positive attitude toward exercise; and social changes such as more coherent social interactions were identified from the analyses.



Commentary by Jon Adams, PhD

This somewhat preliminary qualitative investigation provides some early promising insights that could help guide more in-depth, substantial future investigations employing both qualitative and quantitative data collection. This work suggests that further study of the possible benefits of such an innovative exercise program, combining a range of modalities from conventional and complementary practice for those with mild to moderate dementia, is warranted.

REFERENCE

Eveline Wu, Barnes DE, Ackerman SL, Lee J, Chesney M, Mehling WE. (2015) Preventing Loss of Independence through Exercise (PLIE): qualitative analysis of a clinical trial in older adults with dementia. *Aging & Mental Health.* 2015;19:4:353-62. DOI: 10.1080/13607863.2014.935290

MASSAGE FOCUSED ON MYOFASCIAL TRIGGER POINTS FOR RECURRENT TENSION-TYPE HEADACHE¹

Tension-type headache is widespread. Myofascial trigger points in pericranial muscles appear to be involved in its pathogenesis. They present as increased tenderness and tender nodules in taut muscular bands. Massage focused on these trigger points has been emphasized in clinical practice and was now investigated in a randomized controlled trial. Altogether 62 patients with at least 2 tension type headaches per week were randomized to receive either myofascial trigger point massage over 6 weeks, placebo (detuned ultrasound and gel), or to a wait-list group (no intervention). The outcome measures were headache frequency, duration, and intensity; pain medication (reported in a diary); participant-perceived clinical change; a pressure-pain threshold at the trigger points; and quality of life

measured in 2 headache-specific questionnaires.

During the intervention period, the frequency of headache significantly decreased under massage as well as placebo but not in the wait-list group. No significant difference could be found between massage and placebo regarding this outcome. Regarding pain intensity, duration of headache, and pain medication, no significant difference was found in any group. A significantly greater clinical improvement was perceived with massage than with placebo or no intervention; similarly, quality of life and the pain threshold improved only with massage.

The authors concluded that the trigger points are important for treatment of tension-type headache and that this condition is responsive to placebo. Its investigation should therefore include placebo controls.



Commentary by Gunver Kienle, Dr med

This trial shows an influence of trigger point–focused massage on tension-type headache. It is of great importance to investigate nonpharmacological treatments for such widespread conditions. This trial was

complex and carefully designed and conducted. Nonetheless, it was very small (about 20 patients per group), which may explain why most outcome parameters failed to show significant results. The authors' conclusion about placebo responsiveness may be judged with caution. The trial was not designed to investigate placebo effects. Finding a placebo that mimics a nonpharmacological treatment is challenging. In this trial, an ultrasound gel was applied in the control group, which may have physiological effects on nerve conduction and skin blood flow due to thermocooling^{2,3} and which, therefore, might have had a specific effect on tension-type headache. This limits conclusions on placebo effects. This umbrella term embraces multiple observations from clinical trials but has been difficult to assess unbiased.^{4,5} Still, choosing an appropriate intervention for control groups in clinical research is of great importance and often a challenge, particularly when investigating pain relief. Beyond this discussion, the trial adds important information on treatment of tension-type headache with trigger point–focused massage.

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THE DAYLIGHT TRIAL: VITAMIN D FOR HYPERTENSION¹

Several observational studies suggest an association between low vitamin D levels and the risk of cardiovascular disease. The DAYLIGHT trial was a rigorously designed, adequately powered, double-blind placebo-controlled randomized trial testing whether high-dose vitamin D supplementation reduced blood pressure in individuals with serum 25-hydroxyvitamin D levels <25 ng/mL, prehypertension (systolic blood pressure 120-139 mm Hg; diastolic blood pressure 80-89 mm Hg) or stage I hypertension (systolic 140-159 mm Hg; diastolic 90-99 mm Hg), and not on blood pressure medication. Four sites in 3 US northern latitude cities randomized 534 adults to vitamin D₃ 4000 IU or 400 IU daily for 6 months. No statistical or clinically significant differences between group or within group were observed for change in systolic or diastolic blood pressure, whether measured by 24-hour ambulatory monitoring or at clinic visits. The investigators also assessed the relationship between change in vitamin D blood level and blood pressure but did not find any significant correlation. Results did not differ by race, body mass index, or time of year treated.



Commentary by Robert Saper, MD, MPH

Many observational studies have suggested associations between low vitamin D levels and a range of important diseases. These data have prompted a host of prospective randomized controlled trials (RCTs) such as the DAYLIGHT trial. With the notable exception of vitamin D for osteoporosis and fracture prevention, the results of most of these trials have unfortunately been disappointing. For example, vitamin D has not shown effectiveness in improving asthma,² osteoarthritis,³ or type 2 diabetes.⁴ Future large expensive RCTs of single dietary supplement interventions such as vitamin D should be considered only when supported by highly promising data from well-designed pilot studies.

REFERENCES

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