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SLEEP DURATION AND MORTALITY RISK

A number of studies have demonstrated an association between sleep duration and all-cause mortality. Data are inconsistent however regarding sleep duration and cause specific mortality. This study assessed the association between self-reported sleep duration and the risks of fatal coronary heart disease, sudden cardiac death, cancer-related death and all-cause mortality.

A representative sample of men, 42 to 61 years of age at baseline, all living in eastern Finland, were studied. Data collected at baseline, occurring between 1984 and 1989, included self-reported sleep duration, tobacco abuse, resting blood pressure, alcohol consumption, body mass index, blood sugar history and blood levels of lipids, lipoproteins, creatinine, C-reactive protein and glucose. The subjects were followed for all-cause coronary heart disease and cancer related deaths occurring by the year 2014.

At baseline, the mean age of the participants was 51.7 years, with an average sleep duration of 9.1 hours. During a median of 25.9 years' follow-up, of the 3,261 participants, 802 deaths occurred. Those in the top quartile of sleep duration, with at least 10.2 hours of sleep per night (a median of 11.5 hours), had a significantly increased risk of all-cause mortality ($p < 0.001$), as compared to those who slept less than eight hours (HR 1.36). This increased risk was noted for coronary heart disease (HR 1.56), sudden cardiac death (HR 1.47) and cancer death (HR 1.39). In the fully adjusted analysis, which included known risk factors, the associations were attenuated, but persisted.

Conclusion: This longitudinal study of middle-aged men found that sleeping more than 10 hours per night is associated with a significantly increased risk of all-cause mortality.

Khan, H., et al. Sleep Duration and Risk of Fatal Coronary Heart

Disease, Sudden Cardiac Death, Cancer Death and All-Cause Mortality. *Am J Med.* 2018, December 131 (12): 1499-1505.

GUT BACTERIA MODULATES ATHEROGENESIS

The distal guts of mammals harbor microbial communities which can affect many of the processes in the human body. Evidence suggests that the gut microbiome modulates the development of atherosclerosis, thought to be a chronic inflammatory disease. Gut microbial fermentation of plant polysaccharides results in the production of short chain fatty acids, including butyrate. As butyrate exhibits anti-inflammatory properties, this study reviewed the association between the butyrate producing bacteria, *Roseburia intestinalis* (*R. intestinalis*), and the development of atherosclerosis.

This animal study used mice that were susceptible to atherosclerosis. Initially, 342 mice were exposed to a high-fat cholesterol diet for 16 weeks. At follow-up, the animals demonstrated a wide range in size of atherosclerotic lesions. Among gut microorganisms associated with plaque size were *R. intestinalis*, which demonstrated the strongest negative correlation. Subsequently, two groups of mice were gavaged with a core microbial community that included eight species commonly found in the human microbiome (a control group) or that same core community plus *R. intestinalis* (a treatment group). At follow-up, compared to the control group, the treatment group exhibited a 30% reduction in lesion development.

Plasma cholesterol levels were not significantly associated with lesion size. To test whether the protective effect of *R. intestinalis* could be modulated by diet, the animals were fed a diet low in complex carbohydrates. This diet eliminated the protective effect of the *R. intestinalis*, with intestinal lesions similar to the control group. Upon

reviewing epigenetic programming, the researchers also found that the treatment group produced an increased abundance of highly methylated forms of Lys 36 on histone H3 and H3.3, among others, suggesting altered susceptibility to atherosclerosis by gene expression.

Conclusion: This animal study found that the butyrate producing bacteria, *R. intestinalis*, interacts with dietary plant polysaccharide to significantly reduce atherogenesis.

Kasahara, K., et al. Interactions Between *Roseburia Intestinalis* and Diet Modulate Atherogenesis in a Murine Model. *Nat Microbiol.* 2018; 3: 1461-1471.

PAIN IS A RISK FACTOR FOR FRAILTY

Estimates of pain in the general population range from 40% in community dwelling elderly to 80% in institutionalized individuals. While studies have demonstrated an association between pain and frailty, it is not clear whether pain is a risk factor for frailty. This literature review and meta-analysis was designed to better understand the association between persistent pain and the incidence of frailty.

From a literature review, five prospective studies were chosen for inclusion, involving 13,120 participants, ranging from 59 to 85 years of age. All studies used assessments of pain and frailty, with a median follow-up of three to eight years. A random effects model meta-analysis was performed to investigate the association between pain and frailty.

The data revealed that participants with pain at baseline had twice the risk of developing frailty at the time of follow-up (relative risk 2.22) compared to those without chronic pain, even after adjusting for confounding risk factors.

Conclusion: This literature review and meta-analysis demonstrates that persistent pain is

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associated with a significantly increased risk of frailty.

Saraiva, M., et al. Persistent Pain Is a Risk Factor for Frailty: A Systematic Review and Meta-Analysis from Prospective Longitudinal Studies. **Age Aging**. 2018, November; 47(6): 785-793.

PAIN AND DELIRIUM IN HOSPITALIZED PATIENTS WITH DEMENTIA

Data have shown that people with dementia are six times more likely to be admitted to the hospital with delirium. Further, delirium is associated with an increased risk of death or further hospitalization within the next 12 months. This study assessed the relationship between pain and delirium in patients with dementia in an acute hospital setting.

All hospitalized patients with a pre-existing, documented dementia were eligible to participate. Patients were screened at hospital admission with the Confusion Assessment Method (CAM). Those without delirium completed a Mini-Mental State Exam (MMSE). Data were gathered every four days, including assessments of dementia, self-reported and observational estimates of pain.

Of the 230 participants, 10% experienced pain at rest and 42% experienced pain during activity. The odds of delirium were 3.26 times higher among those with pain at rest ($p = 0.044$), with no increased risk among those with pain during activity. Over half of those with delirium who were unable to report pain were judged to be in pain during activity. No significant difference was seen in the occurrence of delirium between those who were prescribed analgesics and those who were not.

Conclusion: This study of patients with dementia found that, during hospitalization, the odds of delirium were over three times higher among those experiencing pain at rest.

Feast, A., et al. Pain and Delirium in People with Dementia in the Acute General Hospital Setting. **Age Aging**. 2018, November; 47(6): 841-846.

NEUROFILAMENT LIGHT PROTEIN AND RISK OF MILD COGNITIVE IMPAIRMENT

Prognostic markers for Alzheimer's disease have included

cerebral spinal fluid amyloid-beta 42 (A β 42), total tau (T-Tau) and phosphorus related tau (P-Tau). Two more recently identified biomarkers are neurofilament light protein (NFL) and neurogranin (NG). NFL is thought to be a marker for subcortical large-caliber axonal degeneration, while NG is believed to be a biomarker for synaptic dysfunction and/or loss. This study investigated whether cerebral spinal fluid levels of NFL and NG are biomarkers of mild cognitive impairment (MCI).

Subjects were a subset of participants in the Mayo Clinic Study of Aging. Data were obtained from 648 individuals without cognitive impairment, all with at least one year of follow-up with cognitive testing. Cerebral spinal fluid was taken by lumbar puncture, with AB42, T-tau, P-tau, NFL and NG measured. The CSF results were compared with the development of MCI at follow-up.

Data were obtained for 648 patients with an average age of 72.3 years. At a median follow-up of 3.8 years, 14.8% progressed to MCI. Those who progressed to MCI were more frequently carriers of an APOE epsilon allele ($p=0.02$). Compared with the lowest quartile of CSF NFL, the highest quartile was associated with a 2.9-fold increased risk of MCI. There was no significant association between increased CSF T-Tau, P-Tau or NG and the risk of MCI.

Conclusion: This prospective study of community dwelling, elderly individuals without cognitive impairment found that elevated levels of neurofilament light protein in the cerebrospinal fluid are associated with an increased risk of developing mild cognitive impairment.

Kern, S., et al. Association of Cerebral Spinal Fluid Neurofilament Light Protein with Risk of Mild Cognitive Impairment among Individuals without Cognitive Impairment. **JAMA Neurol**. 2018; doi:10.1001/jamaneurol.2018.3459.

DYNAMIC BALANCE AND CONCUSSION

The Centers for Disease Control and Prevention estimates that up to 3.8 million concussions occur annually in the United States. Studies have shown that a history of concussion increases an athlete's risk of sustaining a subsequent concussion. This study investigated the association between dynamic balance performance and concussion injury.

Subjects were 109 elite Irish rugby players. All participants underwent a baseline Y Balance Test (YBT), with an inertial sensor. The outcome variable of interest was the diagnosis of concussion during the ensuing season, with that diagnosis made using the Head Injury Assessment Tool (HIA) in compliance with the world rugby guidelines. Recorded for each player was a self-reported concussion history, playing position, age group and dynamic balance variables.

At baseline, 40% of the players reported of history of concussion, while 19.3% of the players sustained a concussion during the study season. There was no significant difference in baseline testing results between those who had a history of concussion and those who did not. Those who sustained a new concussion demonstrated significantly worse dynamic balance when reaching in the anterior direction, as compared to the non-concussed group. A regression model revealed that, when controlling for concussion history, those with poor balance performance were at a 3.63 greater risk of sustaining a concussion, as compared with those with optimal balance performance.

Conclusion: This study of elite rugby players found an association between reduced dynamic balance performance and the risk of sustaining another concussion.

Johnston, W., et al. Association of Dynamic Balance with Sports-Related Concussion. **Am J Sport Med.** 2019, January; 47(1): 197-205.

SURGICAL OPTIONS FOR MERALGIA PARESTHETICA

Meralgia paresthetica (MP) is a symptomatic entrapment neuropathy of the lateral femoral cutaneous nerve (LFCN). The most common cause is an iatrogenic compression or injury of the LFCN. Treatment can be conservative or surgical, although no consensus has been established regarding the appropriate intervention. This study reviewed the outcomes of patients undergoing surgical intervention.

This retrospective study included 13 patients with MP undergoing surgery between 2012 and 2017. All had previously been unsuccessfully treated by conservative interventions. To establish the diagnosis, patients were assessed with the Pelvic Compression Test, the Tinel's Test, Electromyography and focal nerve

blocks. All underwent surgical intervention with the nerve liberated from fascial adhesions.

Data were complete for 13 patients with an average of 59.1 years, of whom 69.2% were female. A significant reduction in pain was noted postoperatively ($p=0.001$). In 61.5% of the cases the symptoms completely resolved within the first three months. In 38.5%, the symptoms partially persisted at three months and resolved at 12 months. There were no recurrences.

Conclusion: This study of patients with recalcitrant meralgia paresthetica found that surgical decompression may be successful, although symptom resolution may be delayed up to 12 months.

Ataizi, Z., et al. Surgical Options for Meralgia Paresthetica: Long-Term Outcomes in 13 Cases. **Br J Neurosurg.** DOI: 10.1080/02688697.2018.1538480.

PROPRIOCEPTIVE TRAINING AND ANKLE SPRAIN

Ankle sprains occur in many sports, and can significantly limit an athlete's performance. While balance training is thought to prevent or treat ankle sprains, the effects of proprioception training are less clear. This literature review and meta-analysis was designed to better understand the effects of proprioceptive training on the risk of ankle sprain.

A literature review was completed for studies of adults, evaluating the effects of proprioception using balance training, as compared with a control condition, on the incidence of ankle sprain. Of the 1,073 studies found in the database, 12 were chosen for the meta-analysis, including 1,722 subjects.

In the meta-analysis, compared to the control condition, balance training resulted in a 38% reduction in the incidence of ankle sprain. Among the studies that examined dynamic neuromuscular control, balance training with proprioceptive training increased the distance reached in the anterior ($p=0.01$), posterolateral ($p=0.0008$) and posteromedial ($p=0.006$) excursion balance tests.

Conclusion: This literature review and meta-analysis supports the conclusion that balance training with proprioceptive training can significantly reduce the risk of ankle sprain and increase balance and joint position sense.

de Vasconcelos, G., et al. Effects of Proprioceptive Training on the Incidence of Ankle Sprain in Athletes: Systematic Review and Meta-Analysis. **Clin Rehabil.** 2018, December; 32 (12): 1581-1590.

VITAMIN D SUPPLEMENTATION AND COGNITION

Epidemiological studies have suggested that deficiencies of certain nutrients may be related to the development of cognitive decline. As deficiencies in vitamin D have been linked to an increased risk of developing dementia, this study explored the effects of vitamin D supplementation on cognition.

This population based, randomized, double-blind, placebo-controlled trial included Chinese adults 65 years of age or older, living independently and not currently taking vitamin supplementation. All subjects underwent a cognitive assessment at baseline and at six and 12 months. The participants were randomized to take a once daily tablet containing either 400 IU of vitamin D₃ or a placebo. Fasting venous blood samples were obtained to determine blood lipid concentration and vitamin D levels.

At follow-up, Full Scale IQ ($p<0.001$), Verbal Scale IQ ($p<0.001$) and Performance IQ ($p<0.001$) scores were significantly higher in the supplementation group. After adjustment, concentrations of triglyceride, total cholesterol, high density lipoprotein and low-density lipoprotein were found to have decreased in the vitamin D group and increased in the placebo group ($p<0.001$).

Conclusion: This study of elderly Chinese adults found that daily vitamin D₃ supplementation resulted in improved cognitive performance over 12 months.

Hu, J., et al. Effects of Vitamin D₃ Supplementation on Cognition and Blood Lipids: A 12-Month Randomized, Double-Blind, Placebo Controlled Trial. **J Neurol Neurosurg Psychiatry.** 2018, December; 89(12): 1341-1347.

BODY MASS INDEX AND LONG-TERM RISK OF REVISION AFTER HIP REPLACEMENT

Studies of the association between body mass index (BMI) and the risk of revision after total hip replacement have produced mixed

results. This study was designed to better understand the effect of BMI on the risk of revision surgery at 11 years following total hip arthroplasty (THA).

Data were prospectively collected for all patients undergoing THA using data from the National Joint Registry, between April of 2003 and December of 2015. Confounding variables included age at the time of the primary THA, gender, physical status classification, year of primary THA, type of hip replacement and fixation. Data concerning mortality at 90 days and revision were recorded at a maximum follow-up of 11.75 years.

For the 415,598 patients followed, the cumulative probability of death at 90 days, was significantly higher in the underweight than in the normal weight group ($p < 0.0005$). In contrast, compared to the normal weight group 90-day mortality was significantly lower in the overweight ($p < 0.0005$), Obese Class I ($p < 0.0005$), and Obese Class II ($p = 0.049$). At ten year follow up, compared to the normal weight group, the cumulative risk for revision was highest in the Obese Class III (6.7%), and significantly higher than the normal group for Obese Class I, Class II and Class III ($p < 0.0005$ for all). Statistical significance was maintained in the adjusted models.

Conclusion: This population based, longitudinal, cohort study demonstrated that, after total hip replacement, elevated body mass index reduces the short-term risk for mortality, but increases the long-term risk for revision surgery.

Mouchti, S., et al. Long-Term Revision and 90-Day Mortality following Primary Total Hip Replacement. *J Bone Joint Surg.* 2018, December 19: 100(24): 2140-2152.

BENEFITS OF STANDING AT WORK

Sedentary behaviors have been associated with an increased risk of chronic disease and mortality. As office workers spend 70 to 85% of their time sitting, this study assessed the effect of a program designed to decrease sitting time at work.

Eligible subjects were office workers, 18 to 70 years of age, who spent at least 75% of their working day in a seated position. The participants were randomized at the office group level. Those in the intervention group received SMaRT work intervention, including a height

adjustable desk and education concerning the consequences of sitting. An electronic cushion provided feedback by vibration regarding sitting time. The control group were not given lifestyle advice, guidance or modified work stations.

The primary outcome measure was change in occupational sitting time, as assessed by an ergometer. Secondary outcomes included physical activity, musculoskeletal health, work-related measures and measures of cognition, mood, and quality of life. The subjects were assessed at baseline and at three, six - and 12-months' follow-ups.

At 12-month follow-up, compared to controls, the intervention group had a reduction in sit time of 83.28 minutes per work day, with prolonged sitting time reduced by 44.93 minutes per work day. At 12 months, the intervention group obtained significantly better scores in job performance and recovery from occupational fatigue, but not in job satisfaction. The intervention group also earned better scores in time management and mental-interpersonal demands than did the control group. The intervention group also demonstrated better scores on the Stroop Color Word Test-Reaction Time, quality of life and anxiety. No significant difference was found between groups in musculoskeletal complaints.

Conclusion: This randomized, controlled study of office workers found that an intervention strategy designed to reduce sitting time can reduce sitting time and improve job performance, working engagement, occupational fatigue, anxiety and quality of life.

Edwardson, C., et al. Effectiveness of the Stand More at (SMaRT) Work Intervention: Cluster Randomized, Controlled Trial. *BMJ*; 2018: 363: K3870

COGNITION IN YOUNG STROKE PATIENTS

Approximately 10% of all strokes occur in adults below 50 years of age. Studies assessing cognition among young stroke patients have reported a higher prevalence of cognitive impairment than in older adults with stroke. This prospective study further investigated the prevalence and course of cognitive dysfunction in young adult stroke patients.

Consecutive patients admitted with an ischemic stroke, ages 18 to 55, were invited to participate. During

the study period, 150 patients were recruited. All underwent baseline neurologic and neuropsychological evaluation, including MRI and assessment of stroke severity.

The mean age of the sample was 44.5 years, with median stroke severity in the mild range. Within three weeks after hospital admission 40% showed impaired cognitive function, including impaired attention. At three months' follow-up, improvement was noted in general cognitive ability, processing speed, attention and flexibility, as well as executive function. However, cognitive deficits were still present in one third of the patients.

Conclusion: This prospective study of patients with an acute ischemic stroke, 55 years of age or younger, found that, at three months, cognitive impairment is present in 40%.

Pinter, D., et al. Prevalence and Short-Term Changes of Cognitive Dysfunction in Young Ischemic Stroke Patients. *Eur J Neurol.* 2018; doi: 10.1111/ene.13879.

CEREBELLAR STIMULATION AND GAIT RECOVERY

After a stroke, the contralesional cerebellum is implicated in functional reorganization of the motor network. In animal models, stimulation of the cerebellar-cortical networks has been found to improve recovery. This study assessed the effect of cerebellar intermittent Omega-burst stimulation (CRB-iTBS), a variation of repetitive transcranial magnetic stimulation (rTMS), on gait recovery after a stroke.

Subjects were adult patients with chronic (over six months), first ever middle cerebral artery ischemic stroke with residual gait and balance impairment. Assessments included the Berg Balance Scale (BBS), the Fugl-Meyer (FM) assessment, the Barthel Index (BI) and gait analysis. A combination of TMS and electroencephalogram was used to determine the patterns of cortical reorganization. The patients were randomized to receive either active or sham CRB-iTBS.

All participants underwent three weeks of daily sham or active CRB-iTBS, coupled with physical therapy. The CRB-iTBS was applied over the contralesional cerebellum. During locomotion analysis, the patients were asked to walk at a comfortable speed. The primary efficacy analysis was the change from baseline in BBS

scores, with secondary endpoints including changes in the FM and BI.

At three weeks, patients in the active group demonstrated greater improvement on the BBS ($p = 0.03$). The treatment group demonstrated significant improvements from baseline by 15.8% at T1 and 23.1% at T2. No significant change was noted in the control group. The gait analysis demonstrated that step width was significantly reduced in the treatment group.

Conclusion: This study demonstrates that cerebellar intermittent omega burst stimulation in patients with chronic stroke can improve gait and balance.

Koch, G., et al. Effect of Cerebellar Stimulation on Gait and Balance Recovery in Patients with Hemiparetic Stroke. Randomized, Clinical Trial. *JAMA Neurol.* 2018; doi:10.1001/jamaneurol.2018.3639.

CALPEPTIN FOLLOWING SUBARACHNOID HEMORRHAGE IN RATS

Calpain is a calcium dependent neural cysteine hydrolase that plays an important role in neuronal death and neurodegeneration. Studies of experimental subarachnoid hemorrhage (SAH) have shown that inhibitors of calpain can reduce related behavioral deficits. This study was designed to determine whether calpeptin, a strong inhibitor of calpain, can reduce deficits exhibited by rats after a SAH.

Subjects were 32 rats with induced SAH, divided into three groups, including a sham group (S), a subarachnoid hemorrhage plus vehicle group (SAH-V) and a subarachnoid hemorrhage plus calpeptin group (SAH-C). The SAH groups received a single intracerebroventricular injection of calpeptin and/or vehicle for 30 minutes prior to a left carotid artery perforation. Neurobehavioral tests were completed at 72 hours post-SAH. The subjects were sacrificed, with the cerebral cortex harvested for intracellular calcium concentration and calpain activity assessment.

Compared to the sham group, those in the SAH-V group had increased levels of intracellular calcium and calpain activity at the basal cortex. Compared with the SAH-V group, the SAH-C group exhibited reduced brain water content, improved neurobehavioral deficits and reductions in activation of caspase-3, caspase-9, caspase-12

polyADP ribose polymerase and in the number of apoptotic neurons in the basal cortex.

Conclusion: This study suggests that calpeptin, an inhibitor of calpain, can be neuroprotective after a SAH through an anti-apoptotic effect.

Zhou, Y., et al. Calpeptin Reduces Neuro-Behavioral Deficits and Neuronal Apoptosis following Subarachnoid Hemorrhage in Rats. *J Stroke Cerebrovasc Dis.* 2019, January; 28 (1): 125-132.

BUTYRATE, DIETARY FIBER AND NEUROINFLAMMATION

Studies have shown that aging results in chronic systemic inflammation, which can accelerate neuroinflammation in the brain. The exact mechanism is not clear, although the overproduction of the pro-inflammatory cytokine interleukin-1 beta ($IL-1\beta$) is known to play a role. As dietary intake is thought to affect this process, this study reviewed the effect of sodium butyrate (NaB), a short-chain fatty acid (SCFA) produced primarily by bacterial fermentation of fiber in the colon, on neuroinflammation.

A group of aged mice were injected with either a saline control or NaB at 1.2 g/kg body weight, as well as saline or LPS at 0.33 mg/kg body weight. At follow-up, the mice were euthanized for tissue analysis, microglial isolation, and RNA isolation. A second group was fed a diet with either a low or high soluble fiber content and underwent a similar post-mortem analysis.

In the first study, immune activation was noted in the microglia after LPS infusion, with increases in $IL-1\beta$, ($p = 0.0005$). When also infused with butyrate the $IL-1\beta$ expression was attenuated ($p = 0.0497$). These findings were also true for the analysis at the hippocampus, and were more pronounced in the aged mice. In the diet study, cecum and colon analysis indicated severe inflammation associated with immune infiltration in aged animals on a low fiber diet. However, aged mice on a high fiber diet had a decrease in this inflammatory infiltrate. Histology scores supported these findings. Compared to the low fiber diet, the high fiber diet decreased gene expression in the microglia, including $IL-1\beta$, $IL-1\alpha$, $IL-6$, $Nlrp3$, $Tlr4$ and Tnf .

Conclusion: This animal study found that sodium butyrate can reduce inflammation and immune reactivity in the microglia of the brain,

supporting a neuroprotective role of high soluble fiber.

Matt, S., et al. Butyrate and Dietary Soluble Fiber Improve Neuroinflammation Associated with Aging in Mice. *Front Immunol.* 2018. <https://doi.org/10.3389/FIMMU.2018.01832>.

VAGUS NERVE STIMULATION, NEUROINFLAMMATION AND MEMORY

Neuroinflammation is thought to be a critical driver of cognitive deficits, with glia cells playing a central role in this process. Recently the "inflammatory reflex" was described, identifying a neural circuit capable of modulating immunity via signaling through the vagus nerve. Since then, vagal nerve stimulation (VNS) has been shown to inhibit tumor necrosis factor-alpha ($TNF-\alpha$), a marker of neuroinflammation. This study explored the effects of VNS using a novel approach to modulate neuroinflammation.

Mice were injected with lipopolysaccharide (LPS) to stimulate neuroinflammation. Before and after injection the mice were evaluated with tests of cognition. Those in the treatment group received percutaneous VNS, while the control group received sham stimulation.

At three hours after LPS injection a significant elevation in $TNF-\alpha$ was noted. When VNS was initiated before LPS delivery, $TNF-\alpha$ was significantly reduced with VNS at 10Hz ($p < 0.001$) and at 20 Hz ($p = 0.0007$). When initiated after the LPS, only the 10Hz stimulation reduced $TNF-\alpha$ ($p < 0.0001$). Tests of cognitive dysfunction, worsened by LPS delivery, were restored with VNS.

Conclusion: This animal study found that neuroinflammation can be reduced with the use of a percutaneously delivered vagus nerve stimulation.

Huffman, W., et al. Modulation of Neuroinflammation and Memory Dysfunction using Percutaneous Vagus Nerve Stimulation. *Brain Stimulation.* 2019, January-February; 12:19-26.

RIVAROXABAN OR ASPIRIN FOR PATENT FORAMEN OVALE

A patent foramen ovale (PFO) is a potential cause of cryptogenic stroke. Studies assessing the benefits of the

closure of PFO, as compared with medical treatment, have favored closure, although those studies have generally enrolled only patients younger than 60 years of age. This literature review and meta-analysis was designed to more broadly understand the efficacy of PFO closure.

This double-blind, randomized trial was completed at 459 centers in 31 countries. All subjects had sustained an embolic stroke of undetermined source (ESUS) between seven days and six months prior to study enrollment. The patients were randomized to receive either Rivaroxaban, 15 mg plus placebo, or aspirin, 100 mg plus placebo, once a daily. The subjects returned for follow-up at one, six and 12 months, and then every six months. The primary efficacy outcome measure was time to recurrent stroke or systemic embolism.

Data were available for 3,609 patients receiving Rivaroxaban and 3,604 receiving aspirin. Recurrent ischemic stroke occurred at a rate of 3.7 events per 100 person years among patients with PFO, as compared to 4.8 events per 100 years in those without PFO ($p=0.33$). No significant difference was found in recurrent ischemic stroke when comparing the Rivaroxaban group to the aspirin group, among those with PFO (HR 0.54) or among those without PFO (HR 1.06). In a meta-analysis of data combining these data with data from two previous trials, the odds ratio for ischemic stroke favored anticoagulation over PFO closure ($p=0.04$).

Conclusion: This study of patients with embolic stroke of unknown origin found that the risk of recurrent stroke, among patients with a patent foramen ovale, is reduced by 50% by using Rivaroxaban or aspirin.

Kasner, S., et al. Rivaroxaban or Aspirin for Patent Foramen Ovale and Embolic Stroke of Undetermined Source: A Prespecified, Subgroup Analysis from the NAVIGATE ESUS Trial. *Lancet Neurol.* 2018, December; 17 (12): 1053-1060.

PREDICTORS OF POST-ARRIVAL DETERIORATION IN ACUTE STROKE

The frequency and outcomes of neurologic deterioration early after stroke have not been well characterized. This study was designed to better understand the predictors and outcomes of neurological deterioration among

patients in the first hours after the identification of stroke symptoms.

Data were analyzed from the Field Administration of Stroke Therapy-Magnesium (FAST MAG) trial. The Glasgow Coma Scale (GCS) was administered before hospital arrival by paramedics, at the time of arrival by emergency department (ED) personnel and later during the emergency department course of care. Ultra-Early Neurologic Deterioration (U-END) was defined as worsening by two or more points on the GCS between ambulance arrival and ED arrival.

Data were completed for 1,690 patients with a mean age of 69.4 years. Of these, U-END occurred in 11.8%. Among those who were assigned a final diagnosis of ICH, early deterioration occurred in 30.8% at three months. A good functional outcome, defined as a Barthel index score of zero to two occurred in 16% among those with U-END and in 56.6% among those without U-END ($p=0.001$).

Conclusion: This study of patients with acute stroke found that deterioration in clinical status between ambulance arrival and emergency department evaluation occurs more frequently in those with intracranial hemorrhage, and is associated with significantly reduced functional independence at three months.

Shkirkova, K., et al. Frequency, Predictors and Outcomes of Pre-Hospital and Early Post-Arrival Neurological Deterioration in Acute Stroke. Exploratory Analysis of the FAST-MAG, Randomized Clinical Trial. *JAMA Neurol.* 2018, November; 75 (11): 1364-1374.

PATENT FORAMEN OVALE CLOSURE AND CRYPTOGENIC STROKE

Approximately 30 to 40% of ischemic strokes have no clear etiology, and are referred to as cryptogenic strokes. While a patent foramen ovale (PFO) has been associated with cryptogenic stroke, studies of the benefit of PFO closure have been inconclusive. This meta-analysis was performed to better understand this issue.

A literature search was completed for studies involving patients with a cryptogenic stroke and a PFO. Those selected compared the outcomes of PFO closure plus medical therapy (PFO-plus) with those of medical therapy (MT) alone.

Studies chosen for the analysis included 3,750 patients with a mean

age of 46 years. Those receiving PFO-plus had a significantly reduced risk of recurrent stroke as compared to those receiving only MT ($p<0.0001$). No significant difference in mortality was noted between the groups.

Conclusion: This study of patients with cryptogenic stroke found that, among those with a patent foramen ovale, treatment with closure plus medical treatment lowers the risk of recurrent stroke, as compared with medical treatment alone.

Sitwala, P., et al. Percutaneous Closure of Patent Foramen Ovale in Patients with Cryptogenic Stroke-An Updated, Comprehensive Meta-Analysis. *Cardiovasc Revasc Med.* 2018. doi.org/10.1016/j.carrev.2018.09.010

DIACUTANEOUS FIBROLYSIS FOR CARPAL TUNNEL SYNDROME

Diacutaneous fibrolysis (DF) is a technique developed from Cyriax deep friction massage principles. While DF has shown promise for treatment of shoulder pain and lateral epicondylitis, no prior studies have assessed its efficacy for carpal tunnel syndrome (CTS) intervention.

This double-blind, randomized, controlled trial included patients with mild to moderate CTS. The participants were randomized to receive DF or sham DF. All treatment subjects were involved in five sessions of 20 minutes' duration, with an interval of two to five days between sessions. A sham group received similar appearing treatment, but with pressure delivered at a superficial level, without generating mechanical traction on the deep fibers of the soft tissue.

The intensive, nocturnal symptoms of the DF group were significantly reduced compared to those of the sham group. Functional capacity of the upper extremity was significantly improved in the DF group as compared to the sham group. This improvement persisted at one-month follow-up. The DF group demonstrated significantly greater improvement in sensory nerve conduction velocity and motor conduction velocity as compared to the sham group.

Conclusion: This study of DF patients with mild-to-moderate symptomatic carpal tunnel syndrome found that, after five sessions, significant improvements were achieved on electrodiagnostic, symptomatic as well as functional measures.

Del Barrio, S., et al Effects of Diacutaneous Fibrinolysis in Patients with Mild to Moderate Symptomatic Carpal Tunnel Syndrome: A Randomized, Controlled Trial. **Clin Rehab.** 2018, December; 32(12): 1645-1655.

LOW CARBOHYDRATE DIET AND ENERGY EXPENDITURE DURING WEIGHT LOSS

According to the carbohydrate-insulin model of obesity, an increased ratio of insulin to glucagon after a meal with a high glycemic load directs metabolic fuels away from oxidation and toward storage in adipose tissue. Studies exploring this model have not produced conclusive results. This study compared the effects of diets varying in carbohydrate to fat ratios on energy expenditure during weight loss maintenance.

This randomized, controlled trial included adults at Framingham State University, studied between August of 2014 and May of 2017. During a run-in phase, energy intake was restricted to promote 12% weight loss over nine to ten weeks. The subjects who successfully lost this weight were randomized to high, moderate or low carbohydrate test diets for a 20-week phase. During this phase, energy intake was adjusted to maintain weight loss. The diets all contained protein at 20% of total calories, varying the energy contributions of carbohydrates at 60%, 40% or 20%, with the remaining calories obtained through fat. Outcome variables were energy expenditure, physical activity and metabolic hormones.

Of the 234 participants in the weight loss phase, 164 achieved the target 12% reduction in weight loss and were included in this randomized trial. Compared with the high carbohydrate diet, change in total energy expenditures were 91 kcal per day greater on the moderate carbohydrate diet and 209 kcal per day greater on the low carbohydrate diet. The data revealed that energy expenditure increased by 52 kcal/d for every 10% decrease in the contribution of carbohydrate to total energy intake ($p=0.002$). This effect was most pronounced among those with high insulin secretion, as measured at pre-weight loss.

Conclusion: This randomized, controlled trial found that, with similar calories and similar protein intake, patients who consume low carbohydrate diets have significantly greater total energy expenditure.

Ebbeling, C., et al. Effects of a Low Carbohydrate Diet on Energy

Expenditure During Weight Loss Maintenance: Randomized Trial. **BMJ.** 2018;363: k4583.

DURABILITY OF ANTIDEPRESSANT RESPONSE OF REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

In cases of recalcitrant depression, repetitive transcranial magnetic stimulation (rTMS) has been shown to be of value as an additional treatment option. The durability of the antidepressant effects of rTMS is not yet clear. This meta-analysis was designed to better understand the efficacy of rTMS over time.

A literature review was completed for studies of rTMS for the treatment of depression. From this search, 23 articles, published between 2002 and 2018, were chosen for inclusion in the review. From the studies were extracted response rates at three, six and 12 months.

After successful rTMS induction, among 732 patients from 18 studies, 66.5% demonstrated a sustained response at month three. Among the patients followed through six months, 52.9% were still responders, while, at 12 months, 46.3% were still responders. A positive predictor of a positive response at both three and six months was the inclusion of maintenance treatment. Compared to those who did not receive maintenance treatment, the response rates of those who received maintenance treatment were 35.8% higher at three months and 58.7% higher at six months.

Conclusion: This systematic review and meta-analysis of studies of patients with depression treated with repetitive transcranial magnetic stimulation found that 66.5% were still responders at three months and 46.3% were responders at 12 months, with these results enhanced by maintenance therapy.

Senova, S., et al. Durability of Antidepressant Response to Repetitive Transcranial Magnetic Stimulation: Systemic Review and Meta-Analysis. **Brain Stim.** 2019, Jan-Feb; 12(1): 119-128.

COMPRESSION SOCKS DURING EXERCISE

While compression garments have been used to improve circulation, similar garments are worn during sports to improve performance. This study assessed

the effect of compression socks worn during a five km run.

This counterbalanced, crossover design study included 12, well-trained, male runners. All were asked to maintain constant dietary patterns prior to each of three sessions. At each session, the runners performed a standardized warmup, followed by a five km timed trial and a one-hour recovery before a second warmup and five km timed trial.

The runners completed one session wearing compression socks for the first warmup and timed trial and one session with no compression socks. Blood lactate concentration was measured, with samples collected at completion of each stage of the warmup protocol, as well as three minutes after completion of the runs.

The declines in run performance between the first and second runs were moderate in the control group and significantly greater than in the compression stockings group ($p<0.01$). No significant difference was found between the conditions on measures of oxygen consumption, blood lactate or calf volume.

Conclusion: This study of well-trained runners found that wearing compression stockings while running can reduce deterioration in performance one hour later.

Williams, N., et al. Wearing Compression Stockings During Exercise Aids Subsequent Performance. **J Science Med Sport.** 2019; 22(1): 123-127.

VIRTUAL REALITY FOR PARKINSON DISEASE

The prevalence of Parkinson's disease (PD) in industrialized countries is 0.3% in the general population. This study evaluated the effects of virtual reality training (VRT) on motor and cognitive recovery in patients with PD.

Subjects were 20 patients with PD, with an average age of 69.4 years, randomly assigned to a control group or a VRT group. All patients were assessed with a neuropsychological battery, including tests of cognition and affect. Those in the VRT group used the BTS-Nirvana (BTS-N), which creates three-dimensional multisensory and interactive simulation, to allow the patient to interact with virtual scenarios. Each treatment session lasted 30 minutes, with three sessions per week for eight weeks.

Those in the VRT group demonstrated greater improvements in cognitive function, including

(Continued from page 2)

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executive and visuospatial abilities, as compared to the control group. Compared with the control group, significantly greater improvement was noted in scores on the Mini-Mental State Exam ($p=0.014$), the Frontal Assessment Battery ($p<0.001$), the WEIGL ($p=0.015$), the Addenbrooke Cognitive Examination (ACE)-Revised ($p<0.0001$), the ACE-R Attention and Orientation subtest ($p<0.001$), the ACE-R Memory subtest ($p=0.034$), the ACE-R Fluency subtest ($p<0.001$), the ACE-R Language subtest ($p=0.016$) and the ACE-R Visual-Spatial subtest ($p<0.0001$).

Conclusion: This small study suggests that rehabilitation using virtual reality could be valuable for the improvement of cognition and behavioral outcomes of patients with Parkinson Disease.

Maggio, M., et al. What About the Role of Virtual Reality in Parkinson Disease's Cognitive Rehabilitation? Preliminary Findings from a Randomized, Clinical Trial. **J Geriatr Psychiatry Neurol.** 2018; November 31 (6): 312-318.

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