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SWEETENED COFFEE CONSUMPTION AND MORTALITY

Previous studies have found an association between coffee intake and a reduced risk of death. Most of these studies did not distinguish between coffee consumed with sugar or artificial sweetener and those consumed without. This study investigated the association between coffee types and mortality.

Data were obtained from the United Kingdom Biobank, a prospective cohort study of 502,524 participants ages 37 to 73, recruited from across the United Kingdom. Those who had participated in an online, 24-hour, dietary recall questionnaire on at least one occasion were eligible for inclusion. Coffee consumers were asked about the types and amount of coffee they usually drank. Mortality data were obtained from death certificates according to the National Health Services Information Center and the National Health Services Central Register, Scotland.

Among the 171,616 participants, 75.8% were coffee consumers. During a median of seven years' follow-up, 3,177 deaths were recorded. The group was divided into five groups according to the number of cups of coffee consumed (>0 to 1.5, >1.5 to 2.5, >2.5 to 3.5, >3.5 to 4.5, and >4.5 drinks per day). Compared to noncoffee drinkers, unsweetened coffee drinkers demonstrated a significantly greater reduction in mortality, with hazard ratios of 0.79, 0.84, 0.71, 0.71, and 0.77, respectively.

The estimates for sugar-sweetened coffee were 0.91, 0.69, 0.72, 0.79 and 1.05, respectively. The association between artificially sweetened coffee and mortality was less consistent and conclusive. The association between coffee drinking and cancer, as well as cardiovascular disease mortality, was largely consistent with all-cause mortality data.

Conclusion: This prospective study found that, compared with no coffee consumption, drinking sweetened or unsweetened coffee resulted in a u-shaped reduced risk of mortality.

Liu, D., et al. Association of Sugar-Sweetened, Artificially Sweetened, and Unsweetened Coffee Consumption with All-Cause and Cause-Specific Mortality. A Large, Prospective, Cohort Study. **Ann Intern Med**. 2022, July; 175: 909-917.

BUCCALLY ABSORBED CANNABIDIOL AND ROTATOR CUFF REPAIR

Arthroscopic rotator cuff repair (ARCR) is one of the most commonly performed orthopedic procedures in the U.S. Due to the opioid epidemic, alternative pain management solutions have been explored. As the endocannabinoid system (ECS) has emerged as a therapeutic target in pain management, this study assessed the efficacy of cannabidiol (CBD) for the treatment of postoperative pain.

Subjects were 100 opioid-naive patients, 18 to 75 years of age, undergoing ARCR. The patients were randomized preoperatively to receive a placebo or a buccally absorbed CBD at 25 or 50 mgs, based upon body weight, three times per day. In addition, all participants received Percocet 5 mg /325 mg as needed one to two tablets every four to six hours. Pain was assessed with a visual analog scale (VAS) multiple times after surgery.

On day one, the mean VAS pain scores were 4.4 in the CBD group and 5.7 in the control group (p=0.04). A subgroup analysis revealed day one pain scores of 3.9 in the 50- mg group, 5.1 in the 25- mg group, and 5.7 in the control group. Patient satisfaction with pain control was higher in the CBD group on both days one (p=0.04) and two (p=0.03). For the remainder of the trial, the CBD group outperformed the control group on all measures of pain and patient satisfaction, although these findings did not reach statistical significance.

Conclusion: This study of patients undergoing rotator cuff surgery found that CBD at 50 mg per dose, three times per day, could reduce pain and increase pain satisfaction.

Alaia, M., et al. Buccally Absorbed Cannabidiol Shows Significantly Superior Pain Control and Improved Satisfaction Immediately after Arthroscopic Rotator Cuff Repair. A Placebo-Controlled, Double-Blinded, Randomized Trial. **Am J Sport Med.** 2022, July 29; 10.1177/03635465221109573.

TIRZEPATIDE FOR THE TREATMENT OF OBESITY

Recent studies have demonstrated that long-acting glucagon-like peptide-1 (GLP-1) receptor agonists and glucose-dependent insulinotropic polypeptide (GIP), may help in regulating energy balance. This study assessed the efficacy of tirzepatide, (a once-weekly subcutaneous injectable peptide with agonist activity at both GIP and GLP-1 receptors) for weight loss.

This phase three placebo-controlled trial included 2,539 adults, with a body mass index (BMI) of ≥30 kg/m^2, or a BMI of ≥27 kg/m^2 or more and at least one weight-related complication. The subjects were randomized to receive a placebo, or tirzepatide 5 mg, 10 mg, or 15 mg administered subcutaneously once per week for 72 weeks. All received lifestyle intervention including counseling sessions to help participants adhere to healthful balanced meals with a deficit of 500 calories per day. The primary endpoints were the percentage change in weight from baseline to week 72.

At week 72, weight loss for those in the placebo, and the tirzepatide 5mg, 10mg, and 15mg groups were 3.1%, 15%, 19.5%, and 20.9% respectively (p<0.001 for all compared with placebo). The absolute weight reductions were 35.5 pounds in the 5mg group, 48.9

pounds in the 10mg group, and 52 pounds in the 15mg group. At week 72, 95.3% of the participants with prediabetes at baseline in the tirzepatide groups had reverted to normoglycemia, as compared with 61.9% of participants in the placebo group.

Conclusion: This study of overweight adults found that a weekly injection of tirzepatide, combined with counseling, resulted in weight loss, ranging from 35.5- 52 pounds.

Jastreboff, A., et al. Tirzepatide Once Weekly for the Treatment of Obesity. **N Engl J Med.** 2022, July 21;387 (3):205-216.

OUT OF HOSPITAL BLOOD PRESSURE IN MAJOR TRAUMATIC BRAIN INJURY

The Excellence in Prehospital Injury Care (EPIC) study of patients with traumatic brain injury (TBI) found that the implementation of out-of-hospital guidelines was independently associated with a marked improvement in survival to hospital discharge. This secondary analysis of the data explored the relationship between systolic blood pressure (SBP) and mortality.

The Arizona State Trauma Registry contains extensive trauma center data on all patients transported to one of 10 level one trauma centers in the state. Data were included from those with a hospital diagnosis of major TBI and the lowest SBP that was recorded prior to the hospital arrival. The primary outcome was in-hospital mortality.

Data were included for 12,169 patients with a lowest out of hospital SBP of 40 to 299mmHg. Of these, 1,462 died. The SBP data were divided into three ranges. The lowest adjusted mortality was found in those with SBPs between 130 and 180 mmHg, with a decreasing rate of adjusted probability of death from 40 to 130mmHg. A rapid increase in mortality was found in those with SBP above 180 mmHg. The patterns for non-mortality outcomes, including length of stay and discharge disposition, varied with SBP in a similar manner.

Conclusion: This study of patients with traumatic brain injury explored the significance of the lowest systolic blood pressure recorded prior to hospital arrival and found that the best in-hospital survival occurred among those with systolic blood pressures of 130-180 mmHg.

Spaite, D., et al. Optimal out of Hospital Blood Pressure in Major Traumatic Brain Injury: A Challenge to the Current Understanding of Hypotension. **Ann Emerg Med.** 2022, July; 80(1): 46-59.

HIGH VERSUS LOW-INTENSITY STRETCHING

Studies have shown that muscle stretching can increase flexibility and decrease muscle-tendon unit stiffness. The American College of Sports Medicine recommends non-painful static stretching (SST) for 15 to 30 seconds to increase flexibility. However, studies have shown that high-intensity stretch with pain can also increase range of motion and decrease changes in stiffness. This study examined the effects of three different incremental stretch intensities.

This randomized, repeated measures, crossover design included 16 male and female college students with no history of lower extremity contraction, lower extremity or back pain, or mobility issues. The treatment groups included SST at 100%, 110%, and 120% pain intensity, as well as a no stretching control, on four separate days. Static passive torque (SPT), hamstring electromyography (EMG) and pain intensity were continuously recorded during SST. Passive torque of the hamstrings was continuously measured by an isokinetic dynamometer. Range of motion (ROM), maximum dynamic passive torque (DPT max), and stiffness were determined from the torque-angle curve obtained from the isokinetic dynamometer and recorded up to 90 minutes after stretching. Subjects rated their pain from zero to 10 on a numeric rating scale (NRS).

ROM increased immediately after stretch at 100%, 110%, and 120% intensity ($p=0.001$), but was unchanged after the control condition. The range of motion improvement lasted for 30 minutes after 100%, 75 minutes after 110%, and 90 minutes after 120% intensity. The magnitude of increase in ROM immediately after stretch was greater in the 120% group than in the 110% group ($p < 0.05$) or the 100% group ($p < 0.05$). The decrease in stiffness lasted for 30 minutes after stretching at 100% intensity, 45 minutes after 110% intensity, and greater than 90 minutes after 120% intensity, with the magnitude of stiffness reduction significantly greater in the 120% group than in the 110% ($p<0.05$) or 100% group ($p<0.05$).

Conclusion: This small study of healthy college students found that stretch intensity beyond the pain threshold amplifies and prolongs stretch-induced flexibility in a dose-response relationship.

Hatano, G., et al. Effects of High-Intensity Stretch with Moderate Pain and Maximal Intensity Stretch without Pain on Flexibility. **J Sports Sci Med.** 2022, June; 21(2), 171-181.

SODIUM GLUCOSE COTRANSPORTER-2 INHIBITERS VERSUS METFORMIN

Sodium-glucose cotransporter-2 inhibitors (SGLT-2i) are a novel category of oral antidiabetic drugs that inhibit renal glucose reabsorption and increase renal glucose excretion, thus lowering plasma glucose levels. This mechanism is insulin-independent, improving glycemic control without promoting hypoglycemia. This study evaluated the risk for cardiovascular events among adults with type 2 diabetes who initiated treatment with first-line SGLT-2i versus metformin in clinical practice.

Data were obtained from two large commercial United States health insurance databases. Eligible persons were over the age of 18, had had at least one diagnosis of type 2 diabetes and had continuous health insurance enrollment with pharmacy benefits for the last 365 days. Those who were prescribed metformin or any SGLT-2i were followed until the occurrence of a study outcome of death, treatment discontinuation, or the end of the study.

Data were reviewed for 9,334 initiators of SGLT-2i and 819,973 initiators of metformin as a first-line treatment for type 2 diabetes. Compared to metformin initiators, SGLT-2i initiators had a similar risk for MI/stroke/mortality, with a hazard ratio of 0.96, and had a lower risk for hospitalization for heart failure/ mortality, with a relative risk of 0.80. Overall, the safety profiles were similar.

Conclusion: This cohort study comparing metformin with SGLT-2i as a first-line treatment for type 2 diabetes found that SGLT-2i was associated with a similar risk for myocardial infarction and stroke mortality and a lower risk of hospitalization for heart failure/ mortality and hospitalization for heart failure.

Shin, H., et al. Cardiovascular Outcomes in Patients Initiating First-Line Treatment of Type 2 Diabetes with Sodium-Glucose Cotransporter 2 Inhibitors versus Metformin. A Cohort Study. **Annals Int Med.** 2022 Jul;175 (7):927-937.

BONE MINERAL DENSITY AFTER AN ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

Previous studies have demonstrated that, after an anterior cruciate ligament reconstruction (ACLR), patients are at an increased risk of developing of osteoarthritis (OA). This study assessed the changes in bone mineral density (BMD) after an ACLR.

Subjects were 33 Division One collegiate athletes who had no previous ACL injuries, a baseline x-ray, and a bone mineral density (BMD) test before and up to 24 months after an ACL reconstruction. BMD was assessed through X-ray absorptiometry scan, with custom regions of interest (ROIs). Least squares mean values of bone mineral density (BMD) at five percent (F5), 15% (F15), and 50% (F50) of the femur's length and five percent (T5), 15% (T15), and 50% (T50) of the tibia's length from before the injury (PRE) to 24 months after the ACLR.

Compared with before the injury, BMD at F15 of the surgical limb was reduced by 0.06 g/cm^2, 0.09 g/cm^2, and 0.09 g/cm^2, at six, 12, and 24 months, respectively (all $p<0.001$). In addition, the BMD at F5 of the surgical limb was reduced by 0.15 g/ cm^2 at six months ($p<0.001$).

Conclusion: At 24 months after anterior cruciate ligament reconstruction, the proximal bone mineral density at the femur remains reduced compared to baseline.

Knurr, K., et al. Changes in Bone Mineral Density of the Femur and Tibia before Injury to 2 Years after Anterior Cruciate Ligament Reconstruction in Division I Collegiate Athletes. **Am J Sports Med.** 2022, Jul; 50(9): 2410-2416.

CROSS COUNTRY SKIING AND ASTHMA

Asthma is a heterogeneous disease characterized by airway obstruction and is usually associated with chronic airway inflammation. This study investigated the relationship between allergic and nonallergic asthma and training volume in competitive cross-country skiers.

Subjects were Finnish cross-country skiers enrolled in national championships or national junior skiing competitions. The participants were queried about self-reported physician-diagnosed asthma, asthma in parents or siblings, and age at asthma diagnosis. Data from the Finnish Digital and Population Data Services Agency were used to identify a control group, matching to the skiers by age, gender, and region of the country in which they lived. The prevalence of asthma was compared between skiers and non-skiers, and within skiers was compared by level of competition. This level was determined by International Ski Federation points (FIS), earned by placing in the top five during the competition.

Data were obtained for 429 skiers with an average age of 16.5 years. Asthma was identified in 9.2% of the controls and 25.9% of the skiers ($p<0.001$). Being a cross-country skier was associated with an increased risk of asthma [Odds Ratio (OR) of 3.47], including an OR of 1.92 for allergic asthma and an OR of 5.05 for non-allergic asthma ($p<0.001$). Among the skiers, the prevalence of asthma was 56.1% in the highest quartile of FIS points. Using multivariate regression analysis, training volume of over 100 hours per year was found to be associated with a higher risk of non-allergic asthma ($p<0.001$).

Conclusion: This study found that competitive cross-country skiers have a greater prevalence of non-allergenic asthma than controls, with the risk increased with increased levels of training.

Maki-Heikkila, R., et al. High Training Volume is Associated with Increased Prevalence of Non-Allergenic Asthma in Competitive Cross-Country Skiers. **BMJ Open Sport Exerc Med.** 2022; 8: 8e001315.

COVID 19 AND HOSPITALIZATION FOR STROKE

Previous studies have suggested that COVID-19 may have increased the risk of stroke by up to 30%. This nationwide Danish study compared the admission rate and 30-day mortality for all patients with stroke and transient ischemic attack (TIA), comparing the year before and the period during the COVID-19 pandemic.

Data were obtained from the Danish stroke registry including all acute stroke and TIA events. These data were reviewed, with the baseline

identified as March of 2019 through March of 2020 (the year before the first pandemic lockdown). These baseline data were compared to subsequent years through January of 2021. The incidence of stroke was compared to baseline, with stroke severity measured by the Scandinavian Stroke Scale.

During the study period, 22,781 patients were admitted with a stroke/ TIA, with a median age of 73.3 years. Compared to the baseline incidence of stroke (2.09 per 1,000 person-years), a seven percent decrease was noted during the first national lockdown, with an incident rate ratio (IRR) of 0.93. For the subsequent periods, the rate increased by five to seven percent. No significant change was found in the rate of severe strokes, mild strokes, or 30-day mortality. An exception was the higher mortality for all strokes during the first lockdown with a risk ratio of 1.3 and an adjusted ratio of 1.17.

Conclusion: This nationwide Danish study found only a minor influence of the COVID-19 pandemic on stroke hospitalizations.

Simonsen, C., et al. COVID-19 Did Not Result in Increased Hospitalization for Stroke and Transient Ischemic Attack: A Nationwide Study. **Euro J Neurol**. 2022, Aug; 29(8): 2269-2274.

ERENUMAB FOR RECALCITRANT MIGRAINE

Chronic migraine can be a disabling disease requiring acute and preventative treatment. Erenumab is a human monoclonal antibody that selectively binds to and inhibits the canonical calcitonin gene-related peptide receptor. It has been approved for the preventative treatment of migraine in adults in the United States and the European Union. However, limited data are available concerning the efficacy and safety of erenumab for those whose prior preventative treatments had failed.

This randomized, 12-week, double-blind, placebo-controlled trial included patients with chronic migraine at 69 sites. After completing 12 weeks of the double-blind treatment, eligible patients were enrolled in the 52-week open-label treatment period (OLTP). Those participants received subcutaneous erenumab, 70 to 140mg, once per month, during the 52-week OLTP. The primary endpoints were the change in monthly migraine days (MMD), monthly acute migraine-specific medication (MSMD) days. Outcomes were compared between those who had never failed (NF) with previous treatments and those who had experienced a treatment failure (TF) with one, two, or three other medications.

Subjects were 609 patients enrolled in the OLTP. At each assessment point, up to week 12, as compared with the control group, those treated with erenumab enjoyed greater mean reductions in MMD and MSMD. In addition, during the 52-week open-label period, compared with placebo, those treated with erenumab had sustained mean reductions in MMD and MSMD relative to the baseline. The proportion of patients in the combined dose group who achieved a ≥50% MMD response at Week 52 of the OLTP was 46.6% for those who had failed at least three medications.

Conclusion: This study of patients with recalcitrant migraine headaches found that the monoclonal antibody, erenumab, was effective in reducing the number of monthly migraine days and the number of migraine-specific medication days.

Ashina, M., et al. Long-Term Efficacy and Safety of Erenumab in Patients with Chronic Migraine in Whom Prior Preventative Treatments Had Failed: A Subgroup Analysis. **Headache.** 2022, May; 62(5): 624-633.

PERSISTENT HEADACHES AFTER WAR-RELATED TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is the signature medical diagnosis of the U.S. wars in Afghanistan and Iraq, occurring in 14-23% of deployed service members. This study assessed the persistence of headaches resulting from deployment -related TBI (DTBI).

The study included retrospective data from medical records of veterans of the Afghanistan and Iraq campaigns who had experienced a DTBI and later joined the Veteran's Administration (VA) program, "Operation New Dawn". A DTBI was defined as self-reported exposure to either direct head trauma or blast injury or both, with either loss of consciousness (LOC) or alteration of consciousness. Concussion-related symptoms were assessed, and the time interval was determined between injury and clinical evaluation. Also, documented were the severity of the TBI and the age at the time of the TBI.

Subjects were 500 veterans with a DTBI, seen at the Operation New Dawn Clinic in the Oklahoma City Veterans Administration. Of these, 95.8% had a headache, of whom 48.3% reported severe/very severe headache burden. The second most common symptom was "difficulty in decisions," noted in 35%. The severity of the DTBI was indicated by the duration of loss of consciousness. The proportion of subjects with severe/very severe symptom intensity increased as the severity of the DTBI increased ($p = 0.043$ to $p = 0.001$). There was no effect of having had a previous TBI on the prevalence of headaches. In addition, there was no relationship between age at injury and the severity or persistence of the DTBI.

Conclusion: This study of veterans of the Iraq and Afghanistan wars has found that, of those with a documented traumatic brain injury, 95.8% reported headaches.

Couch, J., et al. Persistence of Headache and its Relation to Other Major Sequelae following Traumatic Brain Injury at Two to Eight Years after Deployment-Related Traumatic Brain Injury in Veterans of Afghanistan and Iraq Wars. **Headache.** 2022, Jun; 62(6): 700-717.

DELIRIUM AND RISK OF DEMENTIA

Although delirium and dementia are two of the most common causes of cognitive dysfunction in the elderly, their interrelationship is poorly understood. This study estimated the cumulative incidence of dementia among those who experience an episode of delirium and explored the factors associated with this relationship.

Data were obtained from the National Health Service (NHS) Greater Glasgow & Clyde (GG&C) Health Board. This retrospective cohort study included patients over the age of 65 who had been diagnosed with an index episode of delirium, but who had not been diagnosed with dementia. From 1996, patients were followed from their first episode of delirium until October of 2020. The primary outcome variable was a diagnosis of dementia.

From the database, 12,949 patients were identified with a relevant index episode of delirium. These were followed for an average of 741 days. Of these, 27% had a subsequent diagnosis of dementia and 45% died without a diagnosis of

dementia. The cumulative incidence of dementia was nine percent at six months,13.6% by one year, 31% by five years, 35.5% by 10 years, and 36.3% by 20 years. The cause-specific hazard of dementia increased with the age of the episode of delirium, from age 65 until age 90 when it plateaued and then decreased.

Conclusion: This large cohort study of patients over 65 years of age with a diagnosis of delirium found that, within five years, 31% would be diagnosed with dementia.

Leighton, S., et al. Delirium and the Risk of Developing Dementia: A Cohort Study of 12,949 Patients. **Neurol, Neurosurg, Psychiat.** 2022; 93(8): 822-827.

TRAMADOL VERSUS NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AFTER PITUITARY SURGERY

Pituitary adenomas are the second most common primary central nervous system tumor. Tumor resection is the first-line treatment for these adenomas. While opioids have been considered the optimal medication for pain control, increasing concerns about their use have led to a growing number of studies concerning alternative medications. This non-inferiority study compared the pain control of tramadol with that of non-steroidal anti-inflammatory drugs (NSAIDS).

This randomized, double-blind non-inferiority trial included patients 18 to 70 years of age with confirmed pituitary adenomas. All underwent surgical resection after which they were randomized to one of two treatment groups. The NSAID group received parecoxib 40mg IV immediately after surgery, followed by loxoprogen 60mg po every 12 hours. The tramadol group received 100mg IV immediately after surgery, and then tramadol 100mg po every 12 hours. Pain was assessed with a 10-point visual analog scale (VAS) five times per day.

Data were obtained for 202 patients, evenly divided between the two treatment groups. The mean VAS scores for the first 24 hours post-surgery were 2.6 for the NSAID group and 3.5 for the tramadol group. The mean scores for the first 48 hours post-surgery were 2.2 in the NSAID group and 3.1 in the tramadol group. The mean VAS scores for the first 72 hours were 1.8 in the NSAID group and 2.6 in the tramadol group. All comparisons for non-inferiority and superiority favored the NSAID group ($p<0.001$ for all).

Conclusion: This prospective study of patients undergoing surgical resection of pituitary adenoma found that, compared to tramadol, non-steroidal anti-inflammatory drugs were superior in reducing pain during the first 72 hours after surgery.

Guo, X., et al. Nonsteroidal Anti-inflammatory Drugs versus Tramadol in Pain Management following Transsphenoidal Surgery for Pituitary Adenomas: A Randomized, Double-Blind, Non-Inferiority Trial. **J Neurosurg**. 2022, July: https://doi.org/10.3171/2021.8.jns211637.

NEUROFILAMENT LIGHT AND COGNITIVE OUTCOME AFTER CARDIAC ARREST

Biomarkers may be used as a surrogate for a brain injury after cardiac arrest. Among these, neurofilament proteins have been found to serve as markers for neuroaxonal injury. This study reviewed the association between neurofilament light (NFL) and neurocognitive outcomes following out-of-hospital cardiac arrest (OHCA).

This study involved a secondary analysis of data from a multicenter trial of cryotherapy for patients with OHCA. Subjects were adults with OHCA, assessed at initial hospitalization for neurocognitive ability and with a physical exam including serum NFL levels. The patients were followed for six months with neurocognitive assessments, including the Cerebral Performance Category (CPC), the Mini-Mental State Examination (MMSE), Cerebral Performance Category (CPC), Two Simple Questions (TSQ), and the Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest (IQCODE-CA).

Serum NFL levels were obtained for 384 subjects. Regression models for serum NFL peak levels at 48 -72 hours post-OHCA found that elevated NFL predicted worse outcomes at follow-up on the CPC ($p<0.001$), the MMSE ($p<0.001$), and the Informant Questionnaire on Cognitive Decline in the Elderly-Cardiac Arrest ($p<0.001$).

Conclusion: This study of patients with out-of-hospital cardiac arrest found that increased serum levels of neurofilament light, collected early in hospitalization, are associated with worse neurocognitive outcomes.

Nordstrom, E., et al. Serum Neurofilament Light Levels Are Correlated to Long-Term Neurocognitive Outcome Measures after Cardiac Arrest. **Brain Inj.** 2022, May 12;36(6):800-809.

SERUM NEUROFILAMENT AND CLINICAL DISABILITY IN MULTIPLE SCLEROSIS

Neurofilaments are major components of the axon, which are released into the extracellular fluid when neuroaxonal damage occurs. This study assessed the predictive value of serum neurofilament light chain (sNfL) in predicting grey matter volume and disability.

This study was a follow-up of an 18-month study reviewing the efficacy of W-3 fatty acid for the treatment of relapsing-remitting multiple sclerosis (MS). Labs were drawn, with sNfL measured at regular intervals. The appearance of new gadolinium-enhancing (Gd+) lesions was assessed monthly between baseline and month nine, and then at months 12 and 24. At the 10-year follow-up visit, brain atrophy was assessed.

The overall mean sNfL level did not predict any long-term MRI or clinical outcome findings or changes in clinical measures from month 24 to the 10-year follow-up. However, higher sNfL levels recorded during the periods of Gd+ lesions predicted lower total grey matter (GM) volume ($p=0.04$) and deep GM volume ($p=0.01$), as well as reduced cortical thickness ($p=0.01$), higher T2 lesion count ($p=0.018$), and higher disability, as measured by the dominant hand Nine-Hole Peg Test ($p=0.004$).

Conclusion: This study of patients with relapsing-remitting multiple sclerosis found that higher serum levels of neurofilament light during episodes of active inflammation were predictive of higher disability at 10 years.

Lie, I., et al. Serum Neurofilament as a Predictor of 10-Year Grey Matter Atrophy and Clinical Disability in Multiple Sclerosis: A Longitudinal Study. **J Neurol Neurosurg Psychiatry**. 2022, August; 93(8): 849 -857.

CAPSAICIN PATCH FOR SPINE PAIN

Among patients with spinal cord injury (SCI), neuropathic pain (NP) has been estimated to be as high as 70%. Capsaicin 8% patch is an FDA-approved pharmacological intervention for the treatment of neuropathic pain associated with

postherpetic neuralgia and diabetic peripheral neuropathy. This study evaluated the efficacy of capsaicin 8% for pain in patients with NP related to SCI.

Subjects were adults with SCI at levels C1 to L2, with a self-report of pain for greater than one year, with a visual analog scale (VAS) of at least three out of 10 at or below the level of the injury. The patients were randomized to receive either a control (0.025% capsaicin) or a treatment patch (8% capsaicin) in two, separate, 12-week treatment periods The patch was placed for 60 minutes per day. The pain was assessed with a VAS score for up to 12 weeks. In addition, assessments were made of the quality of life and function.

This pilot study included 11 patients with SCI. Compared to the controls, pain scores in the 8% treatment group improved significantly more over time ($p<0.00087$). Significant improvement was seen at two weeks and four weeks, with a decrease in pain intensity of 35% at week two and 29% at week four with no significant difference beyond four weeks. In addition, SCIM mobility subscale demonstrated significantly greater improvement on the SCI mobility subscale ($p=0.023$).

Conclusion: This pilot study of patients with spinal cord injury and neuropathic pain found that a capsaicin eight percent patch for one hour per day for 12 weeks was effective in reducing pain.

Olusanya, A., et al. Capsaicin Eight Percent Patch for Spinal Cord Injury Focal Neuropathic Pain: A Randomized, Controlled Trial. **Pain Med.** 2022, July doi: 10.1093/pm/pnac104.

EARLY POST-STERNOTOMY CARDIAC REHABILITATION EXERCISE TRAINING

The British Association for Cardiovascular Prevention and Rehabilitation recommends early cardiac rehabilitation (CR), although the timing is not well defined. This study investigated the effectiveness and safety of cardiac rehabilitation exercise training beginning two weeks after sternotomy, as compared with usual care (six weeks).

The Early Initiation of Poststernotomy Cardiac Rehabilitation Exercise Training (SCAR) study was conducted in a real-world UK National Health Service outpatient CR service. Subjects were patients, 18 to 90 years of age, who had undergone coronary artery bypass graft and mitral/aortic valve replacement /repair and were recovering from median sternotomy. All patients were exposed to eight weeks of, supervised, cardiac rehab exercise training, starting at either two weeks (early) or six weeks (standard) post-surgery. Both groups received home exercise training, including short bouts of light to moderate intensity walking, progressing in duration each week. The supervised exercise included warm-up exercises, followed by 20 to 40 minutes of moderate-intensity continuous cardiovascular exercise at 40 - 70% of heart rate reserve. The primary outcome measure was the change in the six-minute walk test (6MWT) distance from baseline to post-rehabilitation.

Data were completed for 158 participants, including 133 males and 25 females. The 6MWT distances were 275 for the early and 247.5 for the usual care ($p=0.16$) subjects, demonstrating non-inferiority. The mean differences between groups for all secondary, including leg and grip strength did not reach statistical significance, again indicating noninferiority.

Conclusion: This prospective study of patients undergoing cardiac surgery found that beginning cardiac rehabilitation within two weeks after cardiac surgery was not inferior to usual care beginning six weeks after surgery.

Ennis, S., et al. Effectiveness and Safety of Early Initiation of Post-Sternotomy Cardiac Rehabilitation Exercise Training Period: The SCAR Randomized, Clinical Trial. **JAMA Cardiol**. 2022 10.1001/jamacardio.2022.1651.

ACE-083 FOR FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Facioscapulohumeral muscular dystrophy (FSHD) is a common form of muscular dystrophy, characterized by slowly progressive and asymmetric weakness in muscles of the face, shoulder, upper arm, lower leg, and trunk. ACE-083 is a recombinant fusion protein linked to the human immunoglobulin G2 Fc domain that functions as a trap for the transforming growth factor (TGF)- β, which inhibits skeletal muscle growth and regeneration. As animal studies using ACE-083 have demonstrated improved muscle hypertrophy and function, this study evaluated its safety and efficacy in human adults with FSHD.

Participants were adults with genetically confirmed FSHD1 or FSHD2. Muscle strength was assessed at baseline, with further valuations using the six-minute walk distances and strength of right ankle dorsiflexion. Part 1 was an open-label, uncontrolled study (three months), evaluating multiple ascending doses of ACE-083 injected into the biceps brachii (BB) or tibialis anterior (TA) muscle, unilaterally or bilaterally.

Part 2 was a randomized, double-blind, placebo-controlled study (six months), followed by a six-month open-label period to evaluate ACE-083 versus placebo, injected bilaterally into either the BB or TA muscle. In the BB trial, the ACE-083 was administered at 150, 200, or 240 mg per muscle. In the TA study, ACE-083 was administered unilaterally at 150mg or 200mg per muscle or bilaterally.

Parts 1 and 2 enrolled 37 and 58 participants, respectively. Total muscle volume increased 16.4% in the BB group ($p<0.001$) and 9.5% in the TA group ($p=0.01$). Despite this, there were no consistent improvements in function or patient-reported outcome measures in either group.

Conclusion: This study of patients with FSHD found that, while ACE-083 improved muscle volume, there were no significant improvements in muscle function or patient-reported outcomes.

Statland, J., et al. Randomized Phase 2 Study of ACE-083, a Muscle-Promoting Agent, in Facioscapulohumeral Muscular Dystrophy. **Musc Nerve.** 2022, July; 66(1): 50-62.

CEREBELLUM STIMULATION AND COGNITION IN ALZHEIMER'S DISEASE

In the last 30 years, clinically approved treatments for Alzheimer's disease (AD) have proven to be of limited efficacy. This study assessed the efficacy of repetitive Transcranial Magnetic Stimulation (rTMS), applied to the cerebellum, for memory and other cognitive impairments in patients with AD.

Subjects were 60 to 80 years of age, with a diagnosis of AD and a Mini-Mental State Examination (MMSE) score of at least 16. At baseline, all were evaluated by neuropsychological assessment, MRI, and cerebrospinal fluid analysis.

The subjects were randomized to receive rTMS or a Sham rTMS (S-rTMS) 20 minutes daily for four weeks at the bilateral cerebellar Crus II. The primary outcome variable was the change in cerebello-cerebral functional connectivity.

After four weeks of treatment, compared to the S-rTMS group, the r-TMS group was found to exhibit enhanced functional connectivity between the right cerebellum Crus II, bilateral DPFC, bilateral medial frontal cortex, and cingulate cortex. Also, compared to the sham group, the rTMS group exhibited improved scores on tests of global cognitive function including the Mini-Mental State Exam, Montreal Cognitive Assessment, and Alzheimer's Disease Assessment Scale-Cognitive section ($p<0.001$ for all). Improvements were noted in the rTMS group for the Rey Auditory Verbal Learning Test of memory ($p=0.008$) the Symbol Digit Modalities Test of attention ($p=0.003$), the Boston Naming Test to assess language ($p=0.007$), and the Trail Making Test-B of executive function ($p=0.018$). The changes in the MMSE relative to baseline were associated with the changes in functional connectivity between the right cerebellum Crus II and the right DLPFC.

Conclusion: This study of patients with Alzheimer's Disease found that cerebellar stimulation using transcranial magnetic stimulation could improve cognitive function in parallel with the improvement of functional connectivity between the cerebellum and the dorsolateral prefrontal cortex.

Yao, Q., et al. Effect of Cerebellum Stimulation on Cognitive Recovery in Patients with Alzheimer's Disease: A Randomized, Clinical Trial. **Brain Stim.** 2022, July-August: 15(4): 910-920.

POST-CONCUSSIVE VESTIBULAR DYSFUNCTION AND THE INFERIOR VESTIBULAR NERVE

Vestibular dysfunction is common among those with persistent post-concussive symptoms (PPCS). This study was designed to establish whether vestibular dysfunction in athletes with PPCS originates from peripheral or central mechanisms.

Subjects were 21 adult athletes with PPCS (>six months) after at least one SRC and 21 control athletes with no previous SRC. Symptoms were evaluated with the Sport Concussion Assessment Tool, 5th edition, (SCAT5) the Dizziness Handicap Inventory, and the Hospital Anxiety Depression Scale. An MRI of the brain was obtained with a 7 Tesla scanner. Tests of peripheral vestibular impairment included the video head impulse test (vHIT), caloric test, cervical vestibular evoked myogenic potentials (cVEMP), and a peripheral pattern of the videonystagmography (VNG). Tests of central vestibular impairment included a central pattern of the VNG (i.e., gaze shifting nystagmus, continuous positional nystagmus), pursuit eye movements (PEM), and posturography.

Compared to controls more SRC patients had abnormal tests on the vHIT ($p<0.001$), cVEMP ($p=0.002$) and VNG ($p=0.072$). The authors note that, the combination of pathology at the posterior semicircular canal in vHIT and the ipsilateral cVEMP suggests an injury to the inferior vestibular nerve, as both are innervated by this nerve. No difference was noted between the groups in cerebellar gray and white matter as evaluated by 7T MRI.

Conclusion: This study found that peripheral nerve dysfunction is associated with vestibular dysfunction in athletes with SRC who have persistent post-concussive symptoms.

Gard, A., et al. Post-Concussive Vestibular Dysfunction is Related to Injury to the Inferior Vestibular Nerve. **J Neurotrauma.** 2022, August;39(11-12): 829-840.

DECOMPRESSIVE CRANIECTOMY FOR TRAUMATIC INTRACRANIAL HYPERTENSION

The Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) evaluated the effectiveness of craniectomy as a last-tier intervention for patients with traumatic brain injury (TBI) and refractory and sustained intracranial hypertension. This study compared surgical and nonsurgical outcomes for up to 24 months.

Patients were 10 to 65 years of age with a TBI and elevated intracranial pressure (>25mmHg), despite conservative intervention. Those subjects were randomized to receive either decompressive craniectomy with medical treatment or without surgery with the option to add barbiturate infusion. The primary outcome measure was the Glasgow Outcome Scale-Extended (GOS-E), recorded for up to 24 months.

The intention-to-treat analyses of outcomes at six, 12, and 24 months included data from 389, 373, and 356 patients, respectively. As compared to the conservative treatment group, GOS-E scores were superior in the surgical group at six, 12, and 24 months ($p<0.001$ for all comparisons). The surgical group demonstrated improvement in GOS-E scores between six and 24 months ($p=0.004$), while the conservative group did not ($p=0.96$).

Conclusion: This study, extending the data from the trial, demonstrates that patients with traumatic intracranial hypertension have a better functional recovery when treated surgically as compared with conservative medical treatment.

Kolias, A., et al. Evaluation of Outcomes among Patients with Traumatic Intracranial Hypertension, Treated with Decompressive Craniectomy versus Standard Medical Care at 24 Months. A Secondary Analysis of the RESCUEicp Randomized Clinical Trial. **JAMA Neurol.** 2022, July; 79 (7): 664-671.

SWITCHING WARFARIN TO A DIRECT ORAL ANTICOAGULANT IN A-FIB

For patients with newly diagnosed nonvalvular atrial fibrillation (AF), direct oral anticoagulants (DOACs) are recommended over warfarin. Medical societies have provided some guidance when considering switching to a DOAC based on time in therapeutic range (TTR): the European Society of Cardiology (TTR <70%), the American College of Chest Physicians (TTR <65%), and the American College of Cardiology (TTR <58%). However, the seminal studies that have led to this conclusion have been based on research comparing DOACs with warfarin in patients whose international normalized ratios (INRs) were within the recommended therapeutic range for 55-68% of the time. This study examined the risk of stroke and major bleeding before and after switching from warfarin to a DOAC, in patient groups by pre-switch TTR guidelines

Data were obtained from the Blue Cross Blue Shield of Michigan-sponsored quality improvement collaborative. Data were retrieved concerning patients initiated on warfarin for non-valvular AF who were later switched to a DOAC between 2010 and 2021. Outcome measures were ischemic stroke and

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major bleeding. The time in therapeutic range (TTR) was calculated by the percentage of blood draws over time within the recommended international normalized ratios (INRs) range over the total time of taking warfarin.

Data were completed for 524 patients. No significant difference was seen between groups in the number of ischemic strokes. The percentage of patients with major bleeding events was 5.9% in the warfarin Group and 12.2% in the DOAC group ($p<0.001$). The DOAC with the least risk of bleeding was Apixaban.

Conclusion: This study of patients with nonvalvular atrial fibrillation who were treated with warfarin found that, after switching to a direct oral anticoagulant, the rates of ischemic stroke were similar, regardless of time in the therapeutic threshold before the switch, although the risk of bleeding was higher in the DOAC group.

Haymart, B., et al. Comparison of Patient Outcomes before and after Switching from Warfarin to a Direct Oral Anticoagulant Based on Time in Therapeutic Range Guideline Recommendations. **JAMA OPEN.** 2022, 5(7): doi: 10.1001/jamanetworkopen. 2022. 22089.

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