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SERUM CAFFEINE CONCENTRATION AT THE TIME OF TRAUMATIC BRAIN INJURY

Caffeine has been shown to be neuroprotective for patients with Parkinson's disease, depression, and Alzheimer's disease. This study assessed the effects of caffeine on the outcomes of patients hospitalized for traumatic brain injury (TBI).

The Pan- Asian Trauma Outcome Study for Traumatic Brain Injury (PATOS-TBI) project was conducted in Korea between December 2018 and June 2020. The subjects were patients seen in the emergency department with a TBI, resulting in cerebral hemorrhage or diffuse axonal injury. Data were collected concerning demographics, socioeconomic status, and comorbidities, and from hospital medical records. Admission serum caffeine levels were compared to Glasgow Outcome Scale (GOS) scores for up to six months after injury, with scores of four and five regarded as a favorable outcome.

An adjusted analysis revealed that, compared to a no caffeine group, the odds ratios (OR) for favorable functional recovery at six months were OR 2.82 in the low, OR 2.18 in the intermediate, and OR 1.59 in the high serum caffeine groups. Compared to the no caffeine group, the ORs for six-month survival were superior in the low (OR 2.38), intermediate (OR 1.62), and high caffeine groups (OR 1.22).

Conclusion: This prospective study of patients seen in the emergency room for traumatic brain injury found that serum caffeine at the time of injury is associated with improved outcomes.

Yoon, H., et al. Serum Caffeine Concentration at the Time of Traumatic Brain Injury and Its Long-Term Clinical Outcome. **J Neurotrauma.** 2023, November; 40 (21-22): 2386-2395.

CARDIOVASCULAR HEALTH SLOWS COGNITIVE DECLINE

Dementia is a major public concern, affecting 55 million people in the world, with this number expected to reach 139 million in 2050. As previous studies have demonstrated that cardiovascular risk factors are correlated with cognitive decline, this study assessed the association between cardiac health behavior and cognitive decline.

The American Heart Association established goals to improve cardiovascular health, known as Life's Essential 8 (LE8). The LE8 includes sleep health, and comprises four health behaviors (diet, physical activity, nicotine exposure, and sleep health) and four other health-related factors (BMI, blood lipids, blood glucose, and blood pressure). This study investigated the association between baseline LE8 scores and cognitive decline.

This Brazilian longitudinal multicenter study evaluated 11,390 civil servants 35-74 years of age at baseline, with the first wave beginning in 2008. Data collection included sociodemographic variables, clinical conditions, occupational history, mental health status, cognitive assessment, imaging, and laboratory examination. From these, individual LE8 scores were calculated. Each underwent tests of memory, verbal fluency, executive function, and depression. Individuals were tested up to three times every four years over a median of eight years.

In the adjusted model, higher baseline LE8 total scores were associated with a lower decline in memory ($p=0.013$), verbal fluency ($p=0.003$), executive function ($p=0.01$), and global cognition ($p< 0.001$). Compared to those with low LE8 scores, those with moderate LE8 scores had a 14% lower cognitive decline and those with high LE8 scores had a 42% slower global cognitive decline period.

Conclusion: This longitudinal study of over 10,000 Brazilian civil servants found that cognition decline was slowed among those who practiced optimal cardiovascular health behaviors.

Firbank, M., et al. Optimal Cardiovascular Health Is Associated with Slower Cognitive Decline. **Eur J Neurol.** 2024, February. 31(2): e16139.

FRAILTY AND NEUROPSYCHOLOGICAL DEFICITS

Frailty is defined as the age-related decline in physiological capacity across several organ systems. This study investigated the relationship between frailty and performance on neuropsychological testing.

Participants were drawn from three large independent cohort studies of dementia and cognitive decline. All participants were 55 years of age or older with sufficient demographic and health data to calculate a frailty index. At baseline, global cognitive functioning was assessed using the mini mental state exam (MMSE). Cognitive status was determined by a clinical assessment in each included study. Individual neuropsychological tests covered several domains. The frailty index was used to operationalize the degree of age-related health deficit accumulation in each data set.

Data were available for 23,819 participants ranging in age from 55 to 104 years. After adjusting for possible cofounders, including age, gender, education, and apolipoprotein epsilon 4, higher levels of frailty were found to be associated with poorer MMSE performance in all samples. The degree to which frailty index scores moderated the relationship between test scores and MMSE scores was assessed. The frailty index score was consistently negative in value and significant across all

neuropsychological tests and study samples.

Conclusion: This study found that frailty is strongly related to the level of cognitive function among older people and is associated with neuropsychological deficits.

Canevelli, M., et al. Frailty is Associated with Clinical Expression of Neuropsychological Deficits in Older Adults. **Euro J Neurol.** 2024; 31: E 16072.

MITHRAMYCIN A FOR NEUROPATHIC PAIN

Pain is mediated, at least in part, by persistent activation and an increase in the number of ligand gated ion channels, expressed as nociceptors. Previous studies have found that Sp1-like transcription factors drive the expression of TRPV1, a pain receptor that is blocked *in vitro* by mithramycin A (MTM). This study assessed the ability of MTM to reverse *in vivo* models of inflammatory and chemotherapy-induced peripheral neuropathy (CIPN) pain and explored MTM's underlying mechanisms.

Subjects were C57Bl/6 male and female mice, eight to twelve weeks of age. The animals underwent intraplantar injections of saline, with or without complete freund adjuvant, to induce inflammatory heat hyperalgesia. To induce CIPN, cisplatin, oxaliplatin (sigma-aldrich), or vehicle (saline) was injected intraperitoneally (3 mg/kg) along with mithramycin A (MTM). The subjects underwent a hargraves thermal heat test, the mechanical paw withdrawal threshold test, and a cold plate withdrawal test.

Mithramycin reversed inflammatory heat hyperalgesia induced by complete freund adjuvant and cisplatin-induced heat and mechanical hypersensitivity. In addition, MTM reversed both short-term and long-term (one month) oxaliplatin-induced mechanical and cold hypersensitivity, without the rescue of intraepidermal nerve fiber loss. Mithramycin reversed oxaliplatin -induced cold hypersensitivity and oxaliplatin-induced TRPM8 overexpression in the dorsal root ganglion (DRG).

Conclusion: This study suggests that neuroplastic changes in pain can be reversed through targeted transcriptional therapeutics such as Mithramycin A.

Xu, Z., et al. Chemotherapy for Pain: Reversing Inflammatory and Neuropathic Pain with the Anti-Cancer Agent Mithramycin A. **Pain.** 2024; 165: 54-74.

SYSTEMIC STEROIDS FOR SCIATICA

While systemic corticosteroids are commonly used to treat sciatica due to lumbar disc herniation (LDH), studies examining the efficacy of this treatment have produced inconsistent results. This literature review and meta-analysis investigated the efficacy of this treatment for sciatic nerve pain.

A literature review was completed for studies including adult patients diagnosed with sciatica, with radiating pain to the thigh or leg, caused by LDH and confirmed by clinical examination or imaging. Eligible studies were placebo-controlled trials involving systemic clinical corticosteroids, with measures including patient reported outcomes such as pain, function, or disability scores and mixed function-capacity-pain scores, as well as health related quality of life.

The literature search produced 54 studies with a total of 1,017 participants with a mean age of 62.5 years. Corticosteroids were administered orally in three trials and parenterally in seven, either by intramuscular or intravenous injection. When pooled, the steroid group demonstrated a superior reduction in pain following treatment, though the effect was weak. When grouped by duration of follow up, a significant reduction in pain was seen only at the immediate and short-term follow-up. The effect of the corticosteroid on function/disability was significant but weak.

Conclusion: This systematic review of studies involving patients with sciatica due to lumbar disc herniation found that the use of systemic corticosteroids was only weakly effective in reducing pain and disability.

Vale, J., et al. The Role of Systemic Steroids in Sciatica Due to Herniated Lumbar Disc. **Spine.** 2023, December 1; 4823: E391-E400.

GENE THERAPY IN AMBULATORY PATIENTS WITH DUCHENNE MUSCULAR DYSTROPHY

Duchene Muscular Dystrophy (DMD) is an X-Linked neuromuscular

disease caused by gene mutations which prevent the production of functional dystrophin. This study assessed the treatment efficacy of delandistrogene moxeparvovec (DM), a recombinant adeno-associated viral (rAAV) vector-based gene therapy, designed to compensate for missing dystrophin.

Twenty eligible, ambulatory males with DMD, four to eight years of age, received a single, intravenous infusion of DM. The number of vector genome copies per nucleus was assessed in muscle tissue to confirm the successful transduction of target cells. The primary endpoint was the change from baseline to week 12 in quantity of DM micro-dystrophin. Muscle function was assessed with the North Star Ambulatory Assessment (NSAA), a 17-item, validated functional rating scale, specifically developed for measuring motor function in ambulatory patients with DMD.

The mean change from baseline to one year in DM microdystrophin was 54.2% ($p<0.0001$). The mean, total NSAA scores in patients treated with DM were 22.1 at baseline and 26.1 at year one ($p<0.0001$). Timed function tests demonstrated improvement at one year with the subjects able to complete all functional assessments more quickly after treatment.

Conclusion: This clinical trial, using commercially processed delandistrogene moxeparvovec demonstrated that a single administration resulted in a significant expression of robust expression of DM micro-dystrophin, an acceptable safety profile, and improved motor function.

Zaidman, C., et al. Delandistrogene Moxeparvovec Gene Therapy in Ambulatory Patients (Aged ≥4 to <8 Years) with Duchenne Muscular Dystrophy: One-Year Interim Results from Study SRP-9001-103 (ENDEAVOR). **Ann Neurol.** 2023, November; 94(5): 955-968.

EFFECTS OF HIGH-INTENSITY FUNCTIONAL TRAINING ON CARDIOMETABOLIC HEALTH

Metabolic syndrome (MetS), a condition that consists of five interconnected cardiometabolic risk factors, has been shown to increase the potential of developing atherosclerotic cardiovascular disease (ASCVD). This study evaluated the efficacy of high-intensity functional training (HIFT) for reducing the global MetS burden.

Subjects were 60 physically inactive adults, 35 to 65 years of age with at least three cardiovascular risk factors for MetS. The 12 weeks of progressive HIFT sessions consisted of four sets, each including four functional exercises, with an RPE exertion level of ≥7, from the following categories: 1) aerobic, 2) lower body strength, 3) upper body strength, and 4) trunk/core strength. The subjects were randomized to groups completing one (HIFT1), two (HIFT2) or three (HIFT3) 55-minute sessions per week.

Improvements from baseline were noted in the metabolic syndrome severity scores (MSSS) in all groups: HIFT1: $d = 0.28$; HIFT2: $d = 1.20$; HIFT3: $d = 1.07$, waist circumference (HIFT1: -4.1cm, $d = 3.33$; HIFT2: -5.4cm, $d = 0.89$; HIFT3: -0.7cm, $d = 0.20$, and blood glucose (HIFT1: -9.5mg/dL, $d = 0.98$; HIFT2: - 4.9mg/dL, $d = 1.00$; HIFT3: -1.7mg/dL, $d = 0.23$). The mean scores on the Physical Activity Enjoyment Scale (PACES) were 5.0-6.1/7 for the three groups.

Conclusion: This study of 60 inactive adults found that high intensity functional training, performed one to three times per week for 12 weeks, can improve cardiometabolic health factors.

Smith, L., A Preliminary Investigation into the Frequency Dose Effects of High-Intensity Functional Training on Cardiometabolic Health. **J Sports Sci Med**. 2023, December; 22(4): 688-699.

OMEGA THREE BLOOD LEVELS AND STROKE RISK

Evidence indicates that one in four adults will suffer a stroke in their lifetime. While scientific evidence has established the cardioprotective effects of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), the effect of these polyunsaturated fatty acids (PUFAs) on the risk of stroke is less clear.

This study was conducted within the Fatty Acid and Outcome Research Consortium, an international collaboration of observational studies, with baseline PUFA biomarker data and follow-up for chronic disease events. Data were pooled from 29 cohorts and included marine omega-3 PUFA biomarker levels from 183,291 individuals with a median follow-up of 14 years. During follow-up, 10,561 cases of incident stroke were recorded. Total stroke, in relation to each PUFA exposure, was analyzed in two models, those with and those without preexisting CVD.

Analysis by quintile of blood levels of DHA revealed that the risks of a stroke in quintile four and five were 12% to 13% lower than that in quintile one. Similar patterns were seen for EPA and EPA+DHA, with the risk in quintile five 17% lower than that in quintile one. The results for hemorrhagic stroke showed little to no evidence of differential risk for any omega-3 PUFA tested.

Conclusion: This study, using data from prospective studies including 183,291 adults, found that docosahexaenoic acid and eicosapentaenoic acid levels are inversely related to the risk of ischemic stroke.

O'Keefe, J., et al. Omega-3 Blood Levels and Stroke Risk: A Pooled and Harmonized Analysis of 183,291 Participants from 29 Prospective Studies. **Stroke.** 2024, January; 55 (1): 50-58.

CARDIAC RISK ESTIMATE OF NONCARDIAC SURGERY

Brain natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) are made by the heart and blood vessels and have been useful in diagnosing heart failure. Guidelines to assess the preoperative risk of non-cardiac surgery have suggested using either NT-pro-BNP or functional capacity, though comparisons of the two are limited. This study compared the discrimination for major adverse cardiac events (MACE) of models including NT-proBNP and validated clinical scores (Revised Cardiac Risk Index [RCRI] and National Surgical Quality Improvement Program, Risk Calculator for Myocardial Infarction and Cardiac [NSQIP MICA], respectively) with models that included self-reported functional capacity and clinical scores.

This multi-center trial included 3,597 consecutive patients, ≥45 years of age, scheduled for elective, inpatient, elevated risk noncardiac surgery. Within 30 days prior to surgery, blood was drawn to sample NT-proBNP concentration. The patients were grouped by concentration including, below 100 pg/mL, 100 to 200 pg/mL, 200 to 1,500 pg/mL, or above 1,500 pg/mL. Self-reported measures of functional capacity consisted of functional capacity in METs (estimated using a

10-item questionnaire), ability to climb one floor, and level of regular physical activity.

At 30 days post-surgery, 103 of 3,593 patients (2.9%) had suffered a MACE. The addition of NT-proBNP to a model of RCRI plus age significantly increased discrimination for in-hospital MACE (p=0.03), but not for 30-day MACE.

Conclusion: This cohort study of 3,597 patients with elevated cardiovascular risk undergoing noncardiac surgery found no conclusive evidence of a difference between a NT-proBNP–based and a self-reported functional capacity–based MACE projection.

Buse, G., et al. NT-proBNP or Self-Reported Functional Capacity in Estimating Risk of Cardiovascular Events after Noncardiac Surgery. **JAMA Network Open**. 2023, November; 6(11): e2342527.

COGNITION FOLLOWING STROKE, TRANSIENT ISCHEMIC ATTACK, AND MYOCARDIAL INFARCTION

Patients with stroke have twice the risk of subsequent cognitive impairment or dementia than those without stroke. This study estimated the years of cognitive aging attributed to transient ischemic attack, myocardial infarction, and hospitalization.

This meta-analysis was completed using data sets from six randomized, controlled trials of vascular risk interventions. All studies had baseline and follow-up data concerning cognition, using either the Mini Mental State Examination (MMSE) or the Montreal Cognitive Assessment (MoCA). Using these scores, the change in cognitive age between baseline and follow-up was measured and compared to that of control subjects.

Data were analyzed for 64,106 patients with an average age of 67 years. The mean MMSE scores were 27.4 at baseline and 25.5 at follow-up among those with a stroke, as compared to 27.8 at baseline and 27.6 for those without a stroke. The mean Montreal Cognitive Assessment scores among those with a stroke were 23.6 at baseline and 22.6 at follow-up, compared with 24.6 at baseline and 24.4 for those without stroke. Converting these findings to cognitive aging, the researchers found that stroke was associated with 18 years of cognitive aging ($p<0.001$), and transient ischemic attack with three years of cognitive aging ($p=0.021$). Myocardial infarction and hospitalization were not significantly associated with cognitive aging.

Conclusion: This study of patients seen in randomized, controlled trials of stroke found that stroke is associated with 18 years of cognitive aging, transient ischemic attack with three years, and myocardial infarction with no significant aging.

Sherlock, L., et al. Cognitive Performance following Stroke, Transient Ischemic Attack, Myocardial Infarction, and Hospitalization: An Individual Participant Data Meta-Analysis of Six Randomized, Controlled Trials. **Lancet Healthy Longev.** 2023, December; 4: E665-E674.

UNDIAGNOSED MAJOR RISK FACTORS IN ACUTE ISCHEMIC STROKE

Identifying, preventing and treating vascular risk factors in the general population before stroke could dramatically reduce the incidence of acute ischemic stroke. This study was designed to assess the vascular risk factors, comorbidities, clinical characteristics stroke etiologies and long-term outcome of patients with acute ischemic strokes comparing those with undiagnosed major vascular risk factors (UMRF) to patients with previously diagnosed major vascular risk factors (DMRF).

This retrospective study included patients participating in the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) between January of 2003 and December of 2018. Vascular risk factors were considered as 'major' according to the INTERSTROKE study, with medical comorbidities collected using the Elixhauser and Charlson indices. The risk factors that were thought to be universally recognized were active smoking, body mass index (BMI) >30 kg/m^2, mechanical valves, depression/psychosis, alcohol abuse and personal history of stroke/TIA/ retinal ischemia. The UMRF were hypertension, dyslipidemia, diabetes, atrial fibrillation, and structural cardiac disease. Each patient was reviewed for newly diagnosed MRF's at the time of the stroke.

Of the 4,354 subjects with a stroke, 25.8% had no previously diagnosed risk factor. Of these 69.7% were found to have an MRF diagnosed at the time of the stroke. Sixty one percent of these were dyslipidemia, 23% hypertension, 10.2% atrial fibrillation and 5.2% diabetes mellitus. At the time of stroke, the median number of undiagnosed MRFs was two in the UMRF group and three in the DMRF group.

Conclusion: This large, single center study of patients with acute ischemic stroke found that prior to the stroke, the patients had a median of 2 -3 previously undiagnosed risk factors.

Rego, A. et al. Undiagnosed Major Risk Factors in Acute Ischemic Stroke Patients: Frequency, Profile, Stroke Mechanisms, and Outcome. **Euro J Neurol.** 2024 Jan;31 (1):e16011.

AGE, BODY MASS INDEX AND INCIDENT STROKE

Previous studies have demonstrated an association between body mass index (BMI) and ischemic stroke. This study assessed the possible effects of age on this association.

The subjects were participants in the Japan Public Health Center (JPHC) prospective study, established in 1990. Data collected included demographic characteristics, lifestyle, and medical conditions, with self-reported height and weight to determine BMI. The BMIs were assigned to one of seven categories (<18.5 kg/m^2, 18.5-<21 kg/m^2, 21-<23 kg/m^2, 23-<25 kg/m^2, 25-<27.5 kg/m^2, 27.5-<30 kg/m^2, and ≥30 kg/m^2). The participants were followed from the baseline survey until the first incidence of stroke, death, or the end of 2009 for cohort I, or 2012 for cohort II, whichever came first.

During a 19-year median follow-up, 4,690 cases of stroke were identified. After adjusting for confounding factors and mediators, BMIs of 27.5-<30 kg/m^2 and ≥30.0 kg/ m^2 were significantly associated with an increased risk of ischemic stroke compared to the reference hazard ratios (HRs). This association was found in both the 40–59-year age group and in those ≥60 years of age. Those with a BMI of < 18.5 kg/m^2 had an increased risk of intracerebral hemorrhage.

Conclusion: This prospective Japanese study found that body mass index was correlated with an increased risk of stroke, with the increased risk beginning with 27.5 kg/ m^2, and not significantly affected by age.

Nuamah, H., et al. The Effect of Age on the Relationship between Body Mass Index and Risks of Incident Stroke Subtypes: The JPHC Study. **J Stroke Cerebrovasc Dis**. 2024, Feb; 33(2): 107486.

EARLY VERSUS DELAYED ANTIHYPERTENSIVE TREATMENT AFTER STROKE

Elevated blood pressure is common among patients with acute stroke and is associated with an increased risk of long-term disability and death. This study assessed the effect of early antihypertensive treatment starting within 48 hours of an ischemic stroke for improving the composite of death and disability.

The China Anti-Hypertensive Trial in Acute Ischemic Stroke (CATIS) study is a multi-center, randomized, open label study conducted in 106 hospitals in China. The subjects were patients ≥40 years of age with an acute ischemic stroke (AIS), diagnosed within 48 hours of symptom onset, with an admission systolic blood pressure (SBP) of between 140-220 mmHg. Those who were randomized to an early treatment group underwent lowering of SBP by 10 to 20% within the first 24 hours. Those in a delayed treatment group discontinued all antihypertensive treatment medications and restarted therapy on day eight with a target SBP of ≤140 mmHg and a target diastolic blood pressure (DBP) of ≤90mmHg. The primary outcome variable was the composite outcome of death within 90 days, or of functional dependency, operationalized as a Rankin Scale score of three to five.

Subjects were 2,413 in the early treatment group and 2,397 in the delayed treatment group. On day seven, the mean SBPs were 139.1 mmHg in the early treatment group and 150.9 mmHg in the delayed treatment group. At day 90, 12.0% of those in the early treatment group and 10.5% in the delayed treatment group had died or had experienced dependency (p=0.08). No significant differences were noted in recurrent stroke or adverse events.

Conclusion: This study of patients with mild to moderate, acute ischemic stroke and admission systolic blood pressure of between 140 mmHg and 220 mmHg did not find that early antihypertensive treatment reduced the odds of dependency or death at 90 days.

Liu, L., et al. Early versus Delayed Antihypertensive Treatment in Patients with Acute Ischemic Stroke: Multicenter, Open Label, Randomized, Controlled Trial. **BMJ.** 2023; 383: e077448.

EXERCISE AND SUPPLEMENTAL OXYGEN FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

For patients with chronic obstructive pulmonary disease (COPD), physical exercise is an evidence based, therapeutic recommendation for all international guidelines. As improving peripheral muscle structure and function represents a key target for pulmonary rehabilitation, this study assessed the impact of supplemental oxygen, combined with exercise training, on peripheral muscle adaptation.

The Salzburg COPD Exercise and Oxygen (SCOPE) study is a prospective, randomized, controlled, double-blind trial in a population with nonhypoxemic COPD. Eligible patients were ≥ 30 years of age, had stable COPD, forced expiratory volume in 1 second (FEV1) between 30% and 60% of predicted, resting arterial oxygen partial pressure (PaO2) >55mmHg and carbon dioxide partial pressure (PaCO2) <45 mmHg. The subjects performed six weeks of combined endurance and strength training three times per week with either supplemental oxygen or medical air provided during training. Functional and aerobic capacity were assessed on a stationary cycle ergometer. Gas exchange parameters were measured with blood draws to measure lactate. Strength and muscle cross sectional area were measured.

After exercise training, the participants demonstrated significant increases in functional capacity, aerobic capacity, exercise tolerance, quadriceps muscle strength, and bilateral CSA. Supplemental oxygen significantly affected the training impact on peak work rate when compared with medical air (p= 0.047). A significant increase in CSA (p= 0.013) was only observed in the training group using oxygen.

Conclusion: This study of patients with stable COPD found that supplemental oxygen during exercise training could increase the peak work rate and improve muscle growth.

Neunhauserer, D., et al. The Impact of Exercise Training and Supplemental Oxygen on Peripheral Muscles in Chronic Obstructive Pulmonary Disease: A Randomized Controlled Trial. **Med Sci Sports Exerc.** 2023, Dec 1;55(12):2123-2131.

LONG-TERM PSYCHOLOGICAL OUTCOMES FOLLOWING STROKE

Previous research concerning the emotional consequences of long-term stroke has predominantly focused on depression. This study was designed to provide a more complete understanding of the prevalence and nature of long-term psychological outcomes following stroke.

The OX-CHRONIC study recruited subjects who had been consecutively recruited from acute stroke wards within the John Radcliffe Hospital in the United Kingdom between 2012 and 2020. Patients who were two or more years post-stroke underwent a battery of neuropsychological tests addressing a range of possible cognitive impairments. Caregivers were also administered measures, including the Caregiver Strain Index, the Informant-GDS, and the Informant Questionnaire for Cognitive Decline in the Elderly (IQ-CODE).

Data were completed for 105 stroke participants (wave one), with 90 completing reassessment one year later (wave two). At wave one, 65.3% were classified as having a domain-general cognitive impairment according to the results of the MoCA, with a score of below 26. When using a stroke specific, multidomain, cognitive cutoff score of 22, the prevalence of impairment was found to be 30.6% at wave one and 34.1% at wave two. On the Oxford Cognitive Screen, 45.9% were found to have at least one cognitive impairment. Attention (27.1%) and executive function (40%) were the most frequently impaired abilities. Elevated depression and anxiety scores were found in 23.5% and 22.5% of the subjects, respectively. Fatigue (51.4%) and apathy (40.5%) rates remained high at wave two.

Conclusion: This study of patients, at least two years post-stroke, found that over half experienced psychological difficulties, including cognition, mood, and fatigue, which impacted long-term quality-of-life.

Kusec, A., et al. Long-Term Psychological Outcomes following Stroke: The OX-CHRONIC Study. **BMC Neurol.** 23, 426 (2023).

Https://Doi.Org/10.1186/S12883-023-03463-5.

TOPICAL CHINESE PATENT MEDICINES FOR CHRONIC MUSCULOSKELETAL PAIN

In the past two decades, chronic musculoskeletal pain (CMP) has become the leading cause of disability worldwide. Topical Chinese patent medicine (CPM) is manufactured from Chinese herbs and processed according to formulas prescribed in the "Fifty-Two Prescriptions for Diseases" (202 B.C. to 9 A.D.), the earliest Chinese prescription book. Evidence of the efficacy of topical CMP for relieving pain is inconsistent. This literature review was designed to better understand the efficacy of CMP for chronic musculoskeletal pain.

A literature review was conducted for studies of patients with pain in the spine, joints, or muscles/tendons. Studies were included if the experimental group received CPM therapies and the control group received only non-Chinese medicine interventions, such as NSAIDs, Voltaren emulsion, or infrared physiotherapy.

Twenty-six randomized, controlled trials were identified, for a total of 3,180 participants, published between 2010 and 2021. The data included 1,528 cases of knee osteoarthritis, 398 cases of arthritis of the shoulder, 34 cases of low back pain, and 320 cases of cervical spondylosis. Sixteen studies found that topical CPM was statistically significantly successful in improving CMP pain (as measured by VAS pain and Womac pain scores) ($p<0.05$). Twelve studies found topical CPMs to be clinically effective (assessed by a 30% or great reduction in symptom severity).

Conclusion: This study of patients with chronic musculoskeletal pain found that topical Chinese patent medicines may provide short-term pain relief.

Tang, K., et al. Topical Chinese Patent Medicines for Chronic Musculoskeletal Pain: Systematic Review and Trial Sequential Analysis. **BMC Musculoskel Disorders.** 2023; 24: 985.

PERCUTANEOUS CORONARY INTERVENTION FOR STABLE ANGINA

Relief from angina is the primary reason that patients with stable coronary artery disease undergo percutaneous coronary intervention (PCI). This study, The Objective, Randomized, Blinded Investigation with Optimal Medical Therapy of Angioplasty and Stable Angina-2 (ORBITA-2), evaluated the effect of PCI in patients with stable angina who were not receiving anti-anginal medications.

This multi-center, double-blind, randomized, placebo-controlled trial was conducted at 14 sites in the United Kingdom. Eligible subjects had angina and at least one vessel with severe ischemic coronary stenosis. Baseline assessments included the Seattle Angina Questionnaire and the EuroQol Group 5 Dimensions 5-Level Questionnaire (EQ-5D-5L). All subjects underwent coronary angiography with invasive physiological assessments. Those with ischemia in at least one vessel were randomized to one of two groups. Those in a PCI group underwent complete revascularization, while a placebo group received no further intervention. The primary endpoint was the Angina Symptom Score (ASS).

Data were analyzed for 301 patients with a mean age of 64 years. At a 12-week follow-up, the mean ASS ratings were 2.9 in the PCI group and 5.6 in the placebo group ($p< 0.001$). The mean daily uses of anti-anginal medication were 0.2 in the PCI group and 0.3 in the placebo group (odds ratio 1.21).

Conclusion: This placebo-controlled trial involving patients with stable angina and ischemic coronary stenosis found that PCI resulted in a lower angina symptom score, indicating a better health status with respect to angina.

Rajkumar, C., et al. A Placebo-Controlled Trial of Percutaneous Coronary Intervention for Stable Angina. **N Eng J Med.** 2023, December 21; 389(25): 2319-2330.

CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY

It is estimated that 60% of patients who receive neurotoxic chemotherapeutic agents develop chemotherapy induced peripheral neuropathy (CIPN). As transcranial electric nerve stimulation (TENS) has been shown to reduce central excitability and to activate descending inhibition, this study assessed the efficacy of this treatment for CIPN.

Subjects were 144 adults with cancer who reported CIPN after treatment with one of four classes of chemotherapeutic agents. Both a treatment and a control group wore the device for five hours per day on a continuous setting every day for six weeks. The TENS in the placebo group device emitted two minutes of stimulation, with a 30-second ramp down of intensity, followed by 57.5 minutes of no stimulation. The primary outcome was the European Organisation for Research and Treatment of Cancer-CIPN20 (EORTC-CIPN20). The main secondary outcome measure was a daily diary of CIPN symptoms.

The EORTC-CIPN20 scores improved by an average of 8.7% in the placebo group and 11.6% in the active group. A subjective sense of improvement was reported by 61% in the active and 42% in the placebo group ($p=0.012$). A subjective improvement in the ability to be active was noted in 42% ($p=0.046$) of the treatment and 26% of the placebo group.

Conclusion: This study of patients with chemotherapeutic cancer induced neuropathic pain found that the daily use of a transcutaneous electrical nerve stimulation device could produce some relief from pain and functional disability.

Gewandter, J., et al. Wireless Transcutaneous Electric Nerve Stimulation (TENS) for Chronic Chemotherapy-Induced Peripheral Neuropathy (CIPN): A Proof-of-Concept, Randomized, Clinical Trial. **J Pain.** 2024; Doi.Org/10.1016/J.Jpain.2023.11.014.

FECAL TRANSPLANT FOR ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the leading cause of dementia. As animal models of AD have implicated the gut microbiota in the pathological features of AD, this study explored the effect of fecal transplant on the symptoms and pathology of AD.

Patients diagnosed with AD and cognitively healthy, control subjects underwent cognitive function and by physical evaluation, including blood draws. Stool samples were collected, and microbiome profiles compared to cognitive testing results. In addition, young male rats underwent microbiome depletion and were then randomized to receive fecal material from the patients with AD (F-AD) or from the control group (C-AD) for

three days. The animals were then followed, with behavioral tests, immunohistochemical studies of the brain tissue, and brain tissue biopsies for amyloid plaque assessment.

For the human subjects with AD, a positive relationship was observed between the mini-mental state exam (MMSE) score and the abundance of Coprococcus, with inverse correlations found for Desulfovibrio, and Dialister. In the rat subjects, a test of modified spontaneous location recognition [a process dependent on adult hippocampal neurogenesis (AHN)] the F-AD recipients were impaired in discriminating between the familiar and novel locations, with impaired long-term spatial memory, and on novel recognition memory tasks, including the novel location recognition test. To assess new neuron survival, BrdU/NeuN labeling found a reduced survival of new neurons and a reduction in dentritic complexity in the F-AD group. The Thioflavin-S fluorescent microscopy of coronal brain sections found an absence of plaque deposition in the hippocampus and cortex, demonstrating that cognition and AHN was altered prior to evidence of extracellular amyloid deposition. In a test of human hippocampal progenitor cells (HPCs) those exposed to serum from AD patients demonstrated a reduction in the expression of Ki67 positive cells, suggesting a decrease in the proliferative capacity.

Conclusion: This study of fecal transplant found that Alzheimer's symptoms can be transferred to healthy young animals via the gut microbiota, thus confirming a causal role of the microbiome in Alzheimer's disease.

Grabrucker, S., et al. Microbiota from Alzheimer's Patients Induce Deficits in Cognition and Hippocampal Neurogenesis. **Brain.** 2023 Dec 1;146(12):4916-4934.

FREMANEZUMAB FOR THE PREVENTATIVE TREATMENT OF MIGRAINE

Fremanezumab is a humanized monoclonal antibody that selectively targets the calcitonin gene related peptide (CGRP) ligand and is approved in Europe for the treatment of migraine. While randomized, controlled trials support treatment effectiveness they often do not capture the complexities of real-world medical practice. The Pan-European Real Life study trial is a large, ongoing, phase-four study, evaluating the real-world effectiveness, safety, and tolerability of this treatment in a diverse European sample.

Subjects were 18 years of age or older, each diagnosed with chronic migraine and prescribed fremanezumab at subcutaneous doses of 225 mg monthly or 675 mg quarterly. The primary effectiveness endpoint was the proportion of participants with at least a 50% reduction from baseline in monthly mean headache days (MMDs) during the six-months after fremanezumab initiation.

Data from 313 participants demonstrated that 55.9% had a 50% or greater reduction in monthly migraine days (MMD) at all timepoints, from months three to 12. At baseline, the mean number of days with acute migraine medication use was 11.1 per month. This fell to a mean of 5.3, 4.6, 4.1, 3.9, and 4.3 days at months one, three, six, nine, and 12, respectively. Headache severity at baseline was 6.1 on an 11-point numeric rating scale. This decreased after initiating treatment with fremanezumab to a mean of 5.2/11, 5.1/11, 4.7/11, 5.0/11 and 4.9/11 at months one, three, six, nine and 12 respectively. The most common adverse events were injection site erythema (5.4%), injection site pruritis (3.3%), and constipation (3.1%).

Conclusion: This large study of patients with chronic migraine headaches demonstrates the efficacy and safety of fremanezumab for migraine prevention in a real-world setting.

Ashina, M., et al. Real-World Effectiveness of Fremanezumab for the Preventive Treatment of Migraine: Interim Analysis of the Pan-European, Prospective, Observational, Phase-Four PEARL Study. **Cephalalgia.** 2023, November; 43(11): 3331024231214987**.**

SURVIVORSHIP OF MENISCAL ALLOGRAFT TRANSPLANTS USING BONE FIXATION

Meniscal allograft transplantation (MAT) has been a treatment option for patients experiencing post-meniscectomy syndrome. This study examined the survivorship and failure rate of patients undergoing MAT.

This retrospective study reviewed prospectively collected data for all MAT procedures at a single institution over 15 years. All participants underwent either medial or lateral MAT surgery and reached a minimum follow-up of two years. The procedures were performed using fresh-frozen, size matched allograft, provided by commercial vendors. All patients underwent MAT, with bone fixation of the graft.

The subjects were assessed with the Lysholm score, Knee Injury and Osteoarthritis Outcome Scores [KOOS], including sub scores, International Knee Documentation Committee [IKDC] scores, and visual analog scale (VAS) scores for pain. Anatomic failure was defined as a tear involving over 20% of the allograph or any peripheral tear and unstable peripheral fixation.

Data were included for 157 patients with a mean age at surgery of 24.9 years and a mean follow-up of seven years. Clinical failure occurred in 8.9% of the knees at a median of 71.2 months. The mean, final IKDC score was 79.6 and the mean, final KOOS values were 89.1 for pain, 77.2 for symptoms, 93.4 for activities of daily living, 72.7 for sports, and 67 for quality of life. The mean VAS score was 1.7 at final follow-up.

Conclusion: This study of patients who underwent MAT surgery with bone fixation found that this procedure has good survival rates and reasonably good clinical outcomes.

Husen, M., et al. Survivorship of 157 Arthroscopic Meniscal Allograft Transplants Using Bone Fixation at a Mean of Seven Years and Prognostic Factors Analysis. **Am J Sports Med.** 2024, January; 52 (1): 96-108.

BLOOD FLOW RESTRICTED VERSUS HIGH INTENSITY RESISTANCE TRAINING OF THE FINGER FLEXORS

Previous studies have demonstrated significant increases in finger flexor strength and endurance after five to ten weeks of training. However, high intensity training (HIT) may increase the risk of upper extremity injury. This study compared the effect of low intensity training (LIT) combined with blood flow restriction (BFR) exercise as an alternative to HIT.

The subjects were 13 low-intermediate rock climbers with a median age of 32.6 years. All completed two, five-week periods of isometric finger flexor training on a hangboard. The crossover design included ten LIT + BFR training exercises at 30% of a one repetition maximum or HIT training sessions at

(Continued from page 2)

60% of max without BFR. Training included both arms performing six sets over two blocks, with one block consisting of three consecutive sets. Maximal voluntary contraction (MVC), force impulse from the four-minute, all-out test (W), critical force (CF), and force impulse above the critical force (W') of the finger flexors were assessed before, after the first, and after the second training period, using a climbing-specific dynamometer.

There was no significant interaction of time and training method, demonstrating no substantial differences between LIT + BFR and HIT. Pairwise comparisons showed significant increases of force impulse only for the HIT method.

Conclusion: This study found that low intensity blood flow restriction exercise was equal to high intensity exercise in maintaining finger flexor strength in rock climbers.

Javorsky, T., et al. Comparing Low Volume of Blood Flow Restricted to High-Intensity Resistance Training of the Finger Flexors to Maintain Climbing-Specific Strength and Endurance: A Crossover Study. **Front Sports Act Living.** 2023; 5: 1256136.

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