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MASK USE AND HEADACHES DURING COVID-19

During the Coronavirus disease 2019 (COVID-19) pandemic, many individuals were required to wear personal protective equipment (PPE), which involved face masks and protective eyewear. This study explored the relationship between the use of face masks and complaints of headaches.

Subjects were 14 years of age or older who had used at least one PPE during the COVID-19 pandemic. All completed a survey of demographic data, PPE usage, previous headache history, new-onset headaches, and individual strategies to minimize headaches.

Data were collected from 5,064 respondents. On average, the participants used a face mask for 26.8 of 30 days, with a mean of 9 1/2 hours per day. Lifelong headache incidence was reported by 98.7% of the respondents, while 72.2% reported having headaches regularly. More than 90% reported headaches worsening following the onset of face mask use. Those with new-onset headaches used PPE for longer periods than those without new-onset headaches ($p<0.001$). The multivariate analysis revealed that predictors of new-onset headaches were a history of previous migraines and a longer mean duration of PPE use.

Conclusion: This study found that the use of face masks worsened headaches among those with pre-existing headaches, with more than half reporting new-onset headaches following face mask use.

Oliveira, R., et al. Headache and the Use of Personal Protective Equipment in the General Population during the COVID-19 Pandemic. **Cephalgia** 2022. 10.1177/03331024211067787.

TIMING OF DIRECT ORAL ANTICOAGULANTS AFTER ATRIAL FIBRILLATION RELATED ISCHEMIC STROKE

For patients with atrial fibrillation (AF), direct oral anticoagulants (DOACs) are at least as effective as vitamin K antagonists (VKAs) in preventing an acute ischemic stroke (AIS). The main advantage of DOACs over VKA is a lower rate of intracranial hemorrhage (ICH). This study evaluated the relative efficacy of DOACs when initiated five days or sooner after an AIS compared to DOACs started later.

This pooled analysis included eight, prospective, European and Japanese cohort studies. Subjects were patients with AIS or TIA, diagnosed with nonvalvular AF who were receiving oral anticoagulation with a DOAC at the time of the event. The patients were grouped by those who continued the DOAC after the event (for those already prescribed an anticoagulant on admission), started a DOAC for those not yet receiving a DOAC, or who stopped and then resumed within 30 days after the index event. The subjects were followed for 30 days for recurrent AIS, ICH, and death. Early DOAC-start (ES) was defined as ≤5days from the index event, with late DOAC-start (LS) defined as >5days.

Data were completed for 2,550 patients with a median age of 77 years. Compared to the LS group, the ES group's average stroke severity was milder, with a mean NIHSS score of four compared to six in the LS group ($p<0.001$). A recurrent AIS after the DOAC was started, occurred in 1.1% of the ES group and 1.2% of the LS group. An ICH occurred in 0.3% of the LS group and 0.1% of the ES group. There was no significant difference between groups in the risk of AIS, ICH, or any stroke.

Conclusion: This study of patients with a TIA or an acute ischemic stroke did not find that early anticoagulation with direct oral anticoagulants increases the risk of intracerebral hemorrhage.

DeMarchis, G., et al. Early Versus Late Start of Direct Oral Anticoagulants after Acute Ischemic Stroke Linked to Atrial Fibrillation: An Observational Study and Individual Patient Data Pooled Analysis. **J Neurol Neurosurg Psychiatry.** 2022; 93: 119-125.

ELASTIC GARMENTS, BLOOD FLOW, EDEMA, AND OXYGENATION

Lower extremity immobility and deep venous thrombosis (DVT) are common among the hospitalized population. Elastic garments are commonly employed to the lower extremities to address this risk. However, the efficacy of these garments is not well understood. This study assessed the effect of eight hours use of non-graduated elastic garments on the blood flow and oxygenation of the lower extremity.

Subjects were nine healthy men who were recreationally active, normotensive, nonsmokers with no history of DVT or cardiovascular disease. During the study procedure, the subjects were asked to engage in an eight-hour seated task. The participants were randomized to wear a lower pressure elastic garment on the right or the left leg from the inguinal region to the ankle joint, with the contralateral lower extremity as a control. Baseline measures included extracellular water content (assessed using multifrequency bioelectrical impedance measurements) flow of the dorsal metatarsal artery, and oxygenation dynamics in the gastrocnemius.

While seated, circumferences of the participant's calf and malleolus were progressively enlarged in the control legs, with no significant change in the garmented legs. A significant increase in extracellular water content in the lower extremities occurred in both limbs, with the percent change significantly higher in the control limbs as compared with the garmented legs. The control legs exhibited significantly lower blood flow of the dorsal metatarsal artery during the eight-hour sessions as compared with the garmented legs ($p<0.05$). Overall, the changes in [oxy-Hb], [total-Hb], and tissue oxygen saturation (SO_2) were higher in the legs with elastic garment than in the control legs.

Conclusion: This study of healthy men found that elastic garment use during a prolonged seated task reduced the onset of edema, reduced the deterioration of tissue

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oxygenation, and protected against reduced arterial blood flow.

Kurosawa, Y., et al. Effects of Prolonged Sitting, with or without Elastic Garments, on Limb Volume Arterial Blood Flow and Muscle Oxygenation. **Med Sci Sports Exer.** 2022, Mar 1;54(3):399-407.

SHOULDER PAIN WITH JOB-RELATED REPETITIVE LOAD

The prevalence of shoulder pain is approximately 25% in the general population. This study was designed to determine the incidence of shoulder pain among novice individuals exposed to repetitive shoulder tasks, and to review the changes in the supraspinatus tendon associated with the development of shoulder pain.

Subjects were dental hygiene (DH) students, chosen as their training involves repetitive upper extremity demands with bilateral static postures and submaximal muscle contractions. The control group were students enrolled in an occupational therapy (OT) program. All were evaluated with a visual analog scale (VAS) for pain, the University of Pennsylvania Shoulder Score (PENN) for shoulder function, and the Hospital Anxiety and Depression Scale (HADS). Ultrasound was used to image the supraspinatus tendon and subacromial space.

Data were complete for 97 participants. At the end of the first academic year, 14 DH students developed shoulder pain, compared to four OT students. Compared with baseline measures, supraspinatus tendon thickness increased by 0.7 mm in the DH-pain group and by 0.2 mm in the DH–no pain group and decreased by 0.2 mm in the OT group ($p<0.01$ for all comparisons). At one year 43% of the DH-pain students and 15% of the DH-no pain group had abnormal anxiety scores ($p=0.03$). The HADS depression scores worsened more in the DH-pain than in the OT group ($p<0.01$) and more in the DH-no pain than in the OT group ($p<0.01$).

Conclusion: This study of dental hygiene students found that the repetitive tasks involved in their training resulted in a significant increase in shoulder pain, with thickening of the supraspinatus tendon. These correlated with increased anxiety and depression scores.

Pozzi, F., et al. Development of Shoulder Pain with Job-Related, Repetitive Load: Mechanisms of Tendon Pathology and Anxiety. **J Shoulder Elbow Surg.** Feb; 31(2): 225-234.

VITAMIN K2 AND D3 ON SPINE FUSION OUTCOME IN PATIENTS WITH OSTEOPOROSIS

As spine fusion depends on the quality and quantity of bone available for harvest, researchers have sought adjunctive treatments to enhance union at the surgical site. As vitamin K2 and vitamin D3 have been used as treatments for osteoporosis, this study assessed the effect of these vitamins on osseous union after spinal fusion surgery.

This prospective, randomized trial included patients with neurologic symptoms due to lumbar degenerative disease who had low bone mass or osteoporosis. Both the control and the treatment group received calcium 1.2 g per day and vitamin D3, 250 units per day. The treatment group also received K2, 45 mg per day. Fusion was assessed by CT at three to six months. A complete intervertebral osseous union was defined as grade I, whereas an incomplete intervertebral fusion was assessed as grade II or III. Clinical outcomes were assessed with the Japanese Orthopedic Association Pain Evaluation Questionnaire (JOA-BPEQ).

Data were complete for 35 patients in the control group and 34 patients in the treatment group. At three months, complete union was found in 88.24% of the treatment group and 68.57% of the control group ($p=0.048$). At six months, these rates were 91.18% and 71.43%, respectively ($p=0.036$). Both groups improved in JOA-BPEQ scores, with no significant difference between the two.

Conclusion: This study of patients with osteoporosis undergoing spinal fusion found that daily ingestion of vitamin K2 and vitamin D3 could improve post-surgical fusion more than vitamin D3 alone.

Zhang, W., et al. Concurrent Treatment with Vitamin K2 and D3 on Spine Fusion in Patients with Osteoporosis-Associated Lumbar Degenerative Disorders. **Spine.** 2022, February 15; 47(4): 352-360.

VITAMIN D SUPPLEMENTATION, LIVER DAMAGE, AND EXHAUSTIVE AEROBIC EXERCISE

Studies have found that hepatic and skeletal muscle damage occurs at the beginning of an exercise program, especially in untrained individuals. This study assessed the effect of vitamin D supplementation

on exercise-induced damage and weight control.

Subjects were 24 untrained men who were randomized to receive either a placebo or 2,000 international units of vitamin D per day. The subjects completed two Bruce aerobic treadmill tests to exhaustion; before starting the Vit D supplementation (or placebo) and after six weeks of intervention. Blood draws to assess liver enzymes and levels of vitamin D occurred before and immediately after the initial exercise program, with subsequent draws before and immediately after the second exercise protocol.

After six weeks, vitamin D levels increased significantly in the experimental group, while a significant decrease was observed in the control group. Compared to the control group, after both treatment one and treatment two, the vitamin D group had lower levels of liver enzymes including ALT (p=0.001, p=0.001), AST (p=0.011, p=0.001), GGT (p=0.018, p=0.001), and ALP (p=0.001, p=0.001). After the second protocol the muscle damage indices (LDH and CK) were significantly lower in the Vitamin D group (p=0.001 for both).

Conclusion: This study of untrained men found that a single bout of exercise could induce increases in muscle liver enzymes and that vitamin D supplementation could decrease this effect.

Mastali, V., et al. The Short-Term Effect of Vitamin D Supplementation on the Response to Muscle and Liver Damage Indices by Exhaustive Aerobic Exercise in Untrained Men: A Quasi-Experimental Study. **BMC Sports Sci Med Rehab.** 2022; 14: DOI: 10.1186/s13102-022-00398-1.

CONTINUOUS PASSIVE MOTION VERSUS PHYSICAL THERAPY AFTER ELBOW CONTRACTURE RELEASE

There is insufficient high-level evidence to determine the optimal rehabilitation protocol after surgical release of an elbow contracture. This study of patients who underwent arthroscopic release of elbow contractures, compared the outcomes of those who received post-surgical continuous passive motion (CPM), to those who received Physical Therapy (PT).

Subjects were consecutive patients with an elbow contracture who were referred for a surgical release. The patients were randomized to receive either CPM or PT. Those in the CPM group were discharged on day three and assigned to a home CPM program. Those in the PT group were referred to a physiotherapist to receive therapy three times per week for four weeks while continuing daily home exercises. The primary outcome was the rate of recovery and the arc of elbow motion at one year. Secondary outcomes were scores on the American Shoulder and Elbow Surgeons (ASES) elbow assessment form, the Disabilities of the Arm, Shoulder and Hand (DASH) score, the Summary Outcome Determination (SOD) score, and the EuroQol-5 Dimension 3-Level, measured up to one year after surgery.

After surgery 24 patients were randomized to the CPM group and 27 to the PT group. At one year the ROM was 114 degrees in the CPM and 105 in the PT group (p=0.007). The CPM group had 13 degrees more ROM at six weeks, 11 degrees at three months, and nine degrees at 52 weeks (p=0.007).

Conclusion: This study of patients who underwent surgical release of an elbow contracture found that rehabilitation with a continuous passive motion machine resulted in a greater recovery of range of motion than rehabilitation with physical therapy.

O'Driscoll, S., et al. Prospective Randomized Trial of Continuous Passive Motion versus Physical Therapy after Arthroscopic Release of Elbow Contracture. **J Bone Joint Surg Am**. 2022; 104(5):430-440.

DAYTIME NAPS, SLEEP APNEA, AND MILD COGNITIVE IMPAIRMENT

Mild cognitive impairment (MCI) is considered a transitional cognitive stage between normal aging and dementia. As apolipoprotein E polymorphism ε4 (APOEε4) is a genetic risk factor for both MCI and Alzheimer's disease (AD), this study assessed the associations between sleep characteristics and APOEε4 with regard to MCI.

This prospective study involved data gathered from Tianjin Elderly Nutrition and Cognition Cohort (TENCC), an ongoing population-based, cohort study focusing on nutrition and cognitive health in older adults in China. Subjects were 3,053 adults, ≥60 years of age, who underwent neuropsychological evaluations that allowed psychometric MCI classification. Information concerning self-reported sleep characteristics was gathered via face-to-face interviews. Fasting venous blood was used to genotype for APOEε4 allele status. In addition, demographic characteristics and lifestyle were documented.

Subjects were 1,705 women and 1,348 men, including 402 participants with new onset of MCI and 2,651 without incident MCI. A greater proportion of non-MCI participants tended to take a nap at noon among APOEε4 non-carriers (p=0.0073). In the multivariable-adjusted models, taking a nap at noon was found to be associated with a decreased risk of MCI in all participants (HR 0.723) and in APOEε4 noncarriers (HR 0.719). Sleep apnea was associated with increased risk of MCI in all participants (HR 2.217).

Conclusion: This study found that the risk of mild cognitive impairment was lessened by noon naps and increased by sleep apnea, especially among APOEε4 noncarriers.

Duan, H., et al. Apolipoprotein E Polymorphism ε4-Stratified Longitudinal Association between Daytime Naps, Sleep Apnea and Mild Cognitive Impairment: A Prospective, Cohort Study. **Euro J of Neurol.** 2022. doi.org/10.1111/ene.15269.

SOCIAL INTEGRATION AND COGNITIVE STATUS

Studies have demonstrated that increased social ties and relationships are associated with lower mortality. Using data from a multi-ethnic cohort of older U.S. adults, this study was designed to better understand the relationship between social integration and cognitive function.

Data were obtained from the Kaiser Healthy Aging and Diverse Life Experiences (KHANDLE), comprising community-dwelling, older adults residing in the San Francisco Bay and Sacramento areas of California. The subjects were chosen to represent approximately equal proportions of Asian, Black, Latino, and White participants, with diverse educational attainment. Data were collected using the Berkman-Syme Social Network Index and the Spanish and English Neuropsychological Assessment Scales (SENAS).

Data were completed regarding 1,343 adults with an average age of 75.4 years. The average integration scores were 3.6 (SD=1.2) for Asian, 3.4 (SD=1.3) for Black, 3.3 (SD=1.2) for Latino, and 3.5 (SD=1.3) for White participants, with no significant differences among groups. A cross-sectional analysis revealed that higher social integration scores were associated with better baseline cognitive scores, with no significant difference seen across racial or

ethnic groups. Social integration was not found to be associated with the estimated rate of cognitive change.

Conclusion: This study revealed that greater social integration, especially frequent interaction with a confidant, is associated with higher baseline cognitive scores.

Calmasini, C., et al. Association of Social Integration with Cognitive Status in a Multi-Ethnic Cohort: Results from the Kaiser Healthy Aging and Diverse Life Experiences Study. **J Geriatr Psychiat and Neurol**. 2022. Jan 25; 8919887211070259. doi: 10.1177/08919887211070259.

MICROBIOTA DYSBIOSIS IN ACUTE ISCHEMIC STROKE

Data demonstrated that microbiota may be involved in the pathology of a wide range of neurologic disorders. This study assessed the microbiota during the acute phase of ischemic stroke, to compare profiles of those with different functional outcomes.

Participants were consecutively recruited from patients seen from May of 2018 through June of 2019, admitted with acute ischemic stroke due to anterior cerebral infarction. Data were collected including demographic and medical histories shortly after admission. Fecal and fasting blood samples were taken within 24 hours of hospital admission.

Functional outcomes were assessed at three months post-stroke using the modified Rankin scale (mRS) score. Genomic DNA was extracted from the fecal samples, with bacterial identification and quantification determined. Serum trimethylamine-N-oxide (TMAO) levels and serum IL- 17, IL-10, and BDNF levels were also determined. The microbiota data were compared between the mRS zero to two (good outcome) and the mRS three to six (poor outcome) groups.

Data were completed for 132 subjects ages 50-91 years. Those in the poor outcome group had less microbiome diversity (p=0.01) and a decrease of beneficial bacteria Bacteroidetes (p=0.12). At the family level, the poor outcome group also demonstrated decreases in Bacteroidaceae, Ruminococcaceae, Veillonellaceae, and Streptococcaceae. Pathogenic bacterium Enterococcaceae was relatively greater in the mRS poor outcome group. Finally, at the genus level, the poor outcome group demonstrated relatively lower levels of SCFA-producing genera (Bacteroides, Faecalibacterium, Roseburia, Ruminococcus, Coprococcus, and Butyricicoccus) Streptococcus and Fusicatenibacter.

Conclusion: This study found that baseline dysbiosis of gut microbiota in patients with acute ischemic stroke correlated with a worse three-month functional outcome.

Sun, H., et al. Gut Microbiota Dysbiosis in Acute Ischemic Stroke Associated with Three-Month Unfavorable Outcome. **Front Neurol**. Published 2022 Jan 28. doi:10.3389/ fneur.2021.799222.

PLANT-BASED DIETS AND HEALTH IN AFRICAN AMERICANS

Observational studies have consistently found that vegetarians and vegans tend to have lower cardiometabolic risk factors and lower risk of heart disease than the general population. This study was designed to better understand the impact of plant-based dietary patterns on the risk of incident cardiovascular disease (CVD) or all-cause mortality in a southern African American population.

The Jackson Heart Study (JHS) prospectively collected data from a community cohort, 21 to 95 years of age, living in the Jackson, Mississippi, metropolitan area, U.S. From 2000 to 2018. The subjects completed a frequency questionnaire (FFQ) at baseline and four subsequent monthly visits. The foods were reviewed for animal food groups, healthy plant food groups, and less healthy plant food groups. The diets were grouped for overall plant-based diet (PDI), healthy PDI (hPDI), and unhealthy PDI (uPDI).

During a median follow-up period of 13 years, no significant association was found between all-cause mortality or CVD and PDI (p= 0.72 and 0.96 respectively), hPDI (p = 0.67 and 0.94 respectively), or uPDI (p = 0.76 and 1.06 respectively). Each additional serving of legumes was associated with a 41% reduction in CVD risk, while each additional serving of healthy oils was associated with a 10% increase in CVD risk. Additional daily servings of whole grains and sugar sweetened beverages were associated with a 13% and 7% increased risk for all-cause mortality, respectively. The authors note that when the diets of the tertiles were assessed with an independent quality metric, even the high hPDI quartile subjects in this population were consuming a poor diet.

Conclusion: Using data from the Jackson Heart Study, researchers found that among this African American population a greater adherence to a plant-based diet was not associated with a reduction in CVD or all-cause mortality.

Weston, L., et al. Plant-Based Diets and Incident Cardiovascular Disease and All-Cause Mortality in African Americans: A Cohort Study. **PLOS Medicine**. 2022. 19(1): e1003863.

RILUZOLE, CEREBRAL GLUCOSE METABOLISM, AND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common neurodegenerative disorder, affecting over 43 million people worldwide. Studies have shown that glutamatergic pyramidal neurons furnish corticocortical connections between association cortical areas and the excitatory hippocampal connections that subserve memory and cognition. This study tested the hypotheses that a glutamate modulator (riluzole) would mitigate the decline of regional cerebral glucose metabolism in AD, that FDG-PET metabolic brain maps would correlate with cognitive measures, and that riluzole would alter the neuronal viability marker, N-acetylaspartate (NAA), and glutamate levels as a marker of target engagement.

Subjects were 15 to 95 years of age with a diagnosis of probable AD and a Mini-Mental State Examination (MMSE) score of 19 to 27. The subjects were randomized to receive either a placebo or riluzole, 50mg BID. The primary endpoints were the change from baseline to six months in cerebral glucose metabolism, as measured with FDG-PET as well as changes in the posterior cingulate (PC) levels of NAA at six months.

Data were completed for 22 patients receiving riluzole and 20 receiving placebo. The decline in FDG-PET cerebral metabolism in several prespecified regions of interest over six months was less in the riluzole group than in the placebo group. The PC glucose metabolism, a primary endpoint, was significantly better in the treatment group at six months ($p<0.0002$). A significant relationship was observed between cognitive measures and cerebral metabolism in FDG-PET, a key measure of brain function in AD.

Conclusion: This study of patients with probable Alzheimer's disease demonstrates that treatment with riluzole slows the decline in glucose metabolism in areas of the brain related to AD-related cognitive decline.

Matthews, D., et al. Riluzole, A Glutamate Modulator, Slows Cerebral

Glucose Metabolism Decline in Patients with Alzheimer's Disease. **Brain.** 2021, December; 144(12): 3742-3755.

ASSISTED MOVEMENT WITH PROPRIOCEPTIVE STIMULATION FOR SUBACUTE STROKE

The most common motor impairment associated with stroke is weakness in finger extension. Previous studies involving patients with hemispheric stroke have shown that robot training is equivalent in therapeutic efficacy to conventional therapy. As muscle vibration has been shown to enhance the sensation of movement and the relaxation of spastic muscles, this study assessed the therapeutic efficacy of combined robot training.

Eligible patients were 18 to 80 years of age with a first cortical or subcortical hemispheric stroke, a baseline Fugl-Meyer upper limb (FMA -UL score (at >5weeks post-stroke)) of 6-43, and voluntary movement of the affected wrist and at least one digit. The subjects were randomized to receive 18, 30-minute sessions of a placebo intervention or robot+vibration training. During robot training, the device provided assisted motion, biofeedback, and antagonist muscle vibration at 80 pulses/second, followed by a ~6-s train of 60 pulses/ s. Assessment measures included the Stroke Impact Scale, the Modified Ashworth Scale, the Ranchos Los Amigos, and FMA-UL. The primary outcome variable was the change in the FMA-UL scores from baseline to follow-up.

Data were completed for 22 participants completing at least 15 training sessions. Compared with the placebo group the test group demonstrated significantly better improvement in FMA-UL scores (p=0.01). The difference in scores between the placebo and the treatment group exceeded the minimally clinically important difference (MCID). In phase II, the crossover group showed significant improvement in FMA UL scores (p=0.003), along with improvements in several upper extremity strength scores.

Conclusion: This study of individuals with moderate to severe upper extremity impairment in the subacute phase of stroke found that robotic training, combined with vibration, produce clinically meaningful gains in function.

Cordo, P., et al. Assisted Movement with Proprioceptive Stimulation Augments Recovery from Moderate to Severe Upper Limb Impairment during Subacute Stroke Period: A Randomized, Clinical Trial. **Neurorehab Neural Repair.** 2022 Jan 24:15459683211063159. doi: 10.1177/15459683211063159. Epub ahead of print.

PREDICTING DEMENTIA USING DIFFUSION TENSOR MRI

Small vessel disease is the most common pathology underlying vascular cognitive impairment and dementia. This is thought to result from the disruption of neuronal networks due to damage to white matter (WM) tracts. As diffusion tensor imaging (DTI) has been shown to be a sensitive method to identify WM ultrastructural damage, this study assessed the efficacy of DTI measures in predicting the onset of dementia.

The OPtimising mulTImodal MRI Markers for use as surrogate markers in trials of Vascular Cognitive Impairment due to cerebrAl small vessel disease (OPTIMAL) collaboration was created to determine whether DTI measures predict dementia in small vessel disease (SVD). Six cohorts with different degrees of SVD severity were included. All underwent MRI at baseline and over three, yearly follow -up sessions. Cognition was measured using a standardized test sensitive to SVD. Processing speed was measured with the Trail Making Test–B. MRIs were processed for brain volume and WMH volume. The ratio of WMH to total cerebral volume (SVDp) was calculated. The relationship between DTI measures and cognition was tested using linear regression.

The mean diffusivity (MD) median was found to correlate with cognition for all cohorts. A higher MD median was associated with a higher risk of dementia after controlling for the clinical markers. The change in MD median over three years predicted dementia conversion over five years.

Conclusion: This study found that white matter alterations play a central role in the pathogenesis of dementia.

Engle, M., et al. Prediction of Dementia Using Diffusion Tensor MRI Measures: The Optimal Collaboration. **J Neurol Neurosurg Psychiatry.** 2022; 93: 14-23.

INTRA-ARTERIAL ALTEPLASE VS PLACEBO FOLLOWING SUCCESSFUL THROMBECTOMY

Endovascular thrombectomy has been found to be an effective treatment for patients presenting with a large vessel occlusion acute ischemic stroke. After thrombectomy, the extent of reperfusion is evaluated on digital subtraction angiography using the modified Treatment in Cerebral Ischemia (mTICI) score. Even with a normal cerebral angiogram, there may remain smaller thrombi within the microvascular bed. The Chemical Optimization of Cerebral Embolectomy (CHOICE) trial assessed the effect of adding adjunct intra-arterial alteplase for those undergoing thrombectomy.

This multicenter randomized double-blind placebo-controlled trial included patients presenting with acute ischemic stroke secondary to a proximal vessel occlusion that resulted in angiographic findings of success (eTICI score of >2b50). The patients were randomized to receive either active treatment with intra-arterial alteplase or placebo. The primary outcome was the difference in the proportion of patients receiving a modified Rankin Scale (mRS) score of zero or one at 90 days.

Of the 113 patients who underwent a thrombectomy, 65 (58%) had an eTICI score of >2b50. A favorable outcome (mRS zero or one) at 90 days was found in 59% in the alteplase group and 40.4% in the placebo group (p=0.047). Death at 90 days occurred in 8.2% of the alteplase and 15.4% of the placebo group. Cerebral hemorrhage was noted in 31.1% of the treatment and 34.6% of the placebo group.

Conclusion: This study of patients with large vessel occlusion acute ischemic stroke and successful reperfusion following thrombectomy found that the use of intra-articular alteplase as an adjunct treatment improved the likelihood of an excellent neurological outcome at 90 days.

Renú, A., et al. Effect of Intra-arterial Alteplase vs Placebo Following Successful Thrombectomy on Functional Outcomes in Patients with Large Vessel Occlusion Acute Ischemic Stroke: The CHOICE Randomized Clinical Trial. **JAMA.** 2022, March 1; Volume 327, Number 9: 826-828.

DOACS VERSUS WARFARIN IN OLDER ADULTS

The efficacy of direct oral anticoagulants (DOACs) in patients with atrial fibrillation (AF) has been well established. Because of the poor representation of older adults with frailty in clinical trials assessing the role of frailty in the choice between these anticoagulants, this study assessed the role of frailty in

the outcome of patients treated with AF treated with an anticoagulant.

This retrospective observational study used Medicare data to emulate three trials using Medicare beneficiaries with AF who filled a prescription for one of three DOACs or warfarin. Eligible participants were 65 years of age or older with frailty measured using a CFI, with frailty defined as a CFI <0.15, prefrailty as CFI of 0.15-0.24 and frailty as 0.25 or greater. For stroke risk the CHA_2DS_2-VASc score was determined for ischemic strokes and HS-BLED for bleeding risk. The primary outcome was a composite of death, ischemic stroke or major bleeding per 1,000 person years. Data were reviewed for three new-user cohorts; dabigatran vs warfarin, rivaroxaban vs warfarin and apixaban vs warfarin.

Over the median follow-up of 82 days, the composite endpoint for the rivaroxaban group was 77.84/1,000 person years, and for the warfarin group 83.7/1,000 person years. A significant difference was found for the nonfrail but not the prefrail or the frail populations. For apixaban initiators the endpoint was 60.1/1,000 person years for the apixaban group and 92.3/1,000 person years for the warfarin users. Significantly better outcomes were found in the frail subgroup than for the non-frail or prefrail. For dabigatran initiators endpoint was 63.5/1,000 person years for the dabigatran initiators and 65.6/1,000 person years for warfarin initiators. This was significant for the non-frail subgroup but not the pre-frail or frail subgroup.

Conclusion: This study of patients with atrial fibrillation found that apixaban was associated with a 32% relative reduction in the hazard of the composite end point of death, ischemic stroke or major bleeding compared with warfarin with reductions of 27% to 39% across frailty subgroups.

Kim, D., et al. Frailty and Clinical Outcome of Direct Oral Anticoagulants versus Warfarin in Older Adults with Atrial Fibrillation. **Ann Intern Med.** 2021, September. 174(9):1214-1223.

SPINAL CORD GRAY MATTER ATROPHY IN POST POLIO

Acute poliomyelitis is caused by a central nervous system infection with the poliovirus. The lower motor neurons of the spinal cord (SC) anterior horn is the area that is mainly affected. After clinical stability is achieved, up to 85% of the survivors will experience a complex of new weakness and atrophy of the previously affected muscles, termed post-polio syndrome (PPS). As the spinal cord gray matter (SCGM) of these patients has not been well studied, this study compared the SCGM of patients with PPS with matched healthy control subjects (HC).

The subjects were 20 patients with PPS and 20 age and sex matched controls. All were assessed with a 3T whole-body MRI scanner. All subjects received a structured clinical examination, including muscle strength assessments of wrist extensors and ankle dorsiflexors. Patient-reported outcomes included the Fatigue Severity Scale (FSS) the Hospital Anxiety and Depression Scale (HADS) and the Chronic Pain Grade Scale (GCPS).

The analysis found significantly reduced SCGM areas in patients with PPS compared to HCs at the intervertebral disc levels close to the cervical and lumbar enlargements. These included C2/C3 ($p = 0.048$), C3/C4 ($p = 0.001$), C4/C5 ($p < 0.001$), C5/C6 ($p = 0.004$) and Tmax ($p = 0.041$). Those reporting PPS-related worsening UL motor function demonstrated significantly reduced SCGM areas at the levels C3/C4, C4/C5, C5/C6 and C6/C7 compared to HC, while patients with stable UL motor function did not.

Conclusion: This study found significant and preferential cervical and thoracic spinal cord gray matter atrophy in patients with post-polio syndrome compared to age- and sex-matched controls.

Wendenbourg, M., et al. Spinal Cord Gray Matter Atrophy is Associated with Functional Decline in Post-Polio Syndrome. **Europ J Neurol**. 2022, February. doi: 10.1111/ene.15261.

ERENUMAB VERSUS TOPIRAMATE FOR MIGRAINE PREVENTION

A recent study demonstrated that 28.2% of migraine patients discontinue treatment within six months, most often due to side effects. As topiramate is thought to have the best evidence supporting its use as a migraine preventive medication, this study compared this medication to a new calcitonin gene-related peptide (CGRP) receptor antagonist, erenumab.

Subjects were 18-65 years of age with a history of migraine for at least 12 months. The subjects were randomly assigned in a 1:1 ratio to either the topiramate group (topiramate verum + erenumab placebo) or the erenumab group (erenumab verum + topiramate placebo). The topiramate group was titrated up with the goal of reaching 100 mg per day. Erenumab was administered as subcutaneous injection every 4 weeks (±4 days) at the study site. The primary outcome was a proportion of patients who discontinued the medication due to an adverse event. A secondary endpoint was a proportion of patients each group who achieved at least a 50% reduction from baseline in MMD over months 4, 5 and 6.

During the 24 weeks of the study the proportion of patients who experienced AEs was 10.6% in the erenumab group and 38.9% in the topiramate group. In the last three months of the study a 50% or greater reduction in MMD was noted in 55.4% of the erenumab and 31.2% of the topiramate group ($p<0.001$).

Conclusion: This study of adults with migraines found that compared to topiramate, treatment with erenumab has a superior tolerability profile and a significantly higher efficacy.

Reuter, U., et al. Erenumab versus Topiramate for the Prevention of Migraine–A Randomized, Double-Blind Active-Controlled Phase 4 Trial. **Cephalalgia.** 2022. https://clinicaltrials.gov/ct2/show/NCT03828539.

BONT-A EFFICACY IN HIGH-FREQUENCY MIGRAINE

Migraine is estimated to affect more than 14% of the population. Based upon the number of monthly migraine days (MMD), high-frequency episodic migraine (HFEM) is associated with an increased risk of transformation into chronic migraine (CM). This study evaluated the efficacy and safety of Onabotulinum toxin-A (BoNT-A) in subjects with HFEM.

Subjects were patients with migraine with a documented frequency of eight to 14 migraine days per month, who had failed previous interventions and had experienced migraine onset after the age of 50. Migraine-associated disability was severe in all patients (migraine disability assessment (MIDAS) grade IV). The subjects received 155 IU BoNT-A in 31 sites, with the treatment repeated three times, 12-weeks apart. All participants completed a headache diary, with MIDAS, migraine-specific questionnaire (MSQ), and Hospital Anxiety and Depression Scale, (HADS) scores obtained at each visit. The primary outcome variable was the reduction of at least two MMD.

For the 28 subjects who completed the trial, the number of MMDs was reduced by 3.68 days on average ($p<0.001$). Thirty-nine

percent of the patients had at least a 50% reduction in migraine days. The MIDAS and MSQ scores significantly improved (p=0.001 and p<0.001, respectively). Only one patient discontinued the study drug due to a mild, self-limiting, cutaneous allergic reaction at the site of injection.

Conclusion: This study of adult patients with high-frequency episodic migraine found that botulinum toxin could reduce the frequency of migraines, the intake of acute medications and the burden of disease.

Martinelli, D., et al. BoNT-A Efficacy in High-Frequency Migraine: An Open -Label, Single-Arm, Exploratory Study Applying the PREEMPT Paradigm. **Cephalalgia.** 2022; 42(2): 170-175.

CONCURRENT USE OF PRESCRIPTION GABAPENTINOIDS WITH OPIOIDS AND ELDERLY FALL-RELATED INJURIES

Gabapentinoids are increasingly prescribed to manage chronic, non-cancer pain in older adults. This study compared the effect of concurrent prescriptions of gabapentinoids and opioids, with that of opioids alone, on the risk for fall-related injury in older adults.

This study used a 5% national sample of Medicare beneficiaries, 65 years of age or older, who were prescribed opioids between January 1, 2011, and December 31, 2018. Cohort one included 6,773 adults who initiated gabapentinoids and opioids simultaneously and compared these with 27,092 opioid-only initiators. Cohort two included 5,709 adults who initiated gabapentinoids with existing opioid use and compared these with 22,388 patients who continued with an opioid-only regimen.

For cohort one, the risk of an incident fall-related injury did not differ between the two groups (Hazard Ratio (HR) 0.97). For cohort two, an increased risk of an incident fall-related injury was observed among patients initiating gabapentinoids with existing opioids, as compared with those continuing opioids only (HR 1.69; p=0.005). For this comparison, the increased fall risk was significant in the first 14 days of concurrent use (p<0.001), but not during days 15 to 30 (p = 0.870).

Conclusion: This analysis of Medicare data found that prescribing gabapentinoids to those with an existing opioid prescription resulted in a 69% increased risk of falls relative to initiating gabapentinoids and opioids simultaneously.

Chen, C., et al. Concurrent Use of Prescription Gabapentinoids with Opioids and Risk for Fall-Related Injury among Older, U.S. Medicare Beneficiaries with Chronic, Noncancer Pain: A Population-Based Cohort Study. **PLOS Medicine**. 2022; 19(3): e1003921. https:// doi.org/10.1371/ journal.pmed.1003921.

CHRONIC ANKLE INSTABILITY IN BASKETBALL ATHLETES

Ankle sprains are among the most common injuries among athletic people. This study investigated the prevalence of chronic ankle instability (CAI) in a group of basketball athletes and explored the factors associated with this chronicity.

Team staff from all semi-professional and college basketball teams in Taiwan were offered enrollment in the study. Those who were enrolled completed a printed questionnaire regarding demographics, history of ankle sprain/giving-way, and recurrent ankle sprain, as well as the Taiwan-Chinese version of the Cumberland Ankle Instability Tool Questionnaire (CAIT-TW).

Data were obtained for 388 basketball athletes, of whom 97 reported an ankle sprain. Of these, 26% had unilateral CAI and 50% bilateral CAI. Only 24% were without CAI. Women had a higher prevalence of CAI than men (p=0.003). The athletes' competitive levels did not correlate with the prevalence of CAI.

Conclusion: This Taiwanese study of elite basketball players found that 97% reported an ankle sprain, among whom 50% reported bilateral chronic ankle instability.

Lin, C., et al. The Prevalence of Chronic Ankle Instability in Basketball Athletes: A Cross-Sectional Study. **BMC Sports Sci Med Rehabil.** 2022;14(1):27.

TRANSCRANIAL DIRECT CURRENT STIMULATION REDUCES SECONDARY HYPERALGESIA

Anodal transcranial direct current stimulation (atDCS) has been found to reduce pain in both healthy and chronic pain populations. Analgesia induced by atDCS over the left dorsolateral prefrontal cortex (L-DLPFC) has been found to correlate with decreased activity in the thalamus and posterior insula, suggesting the involvement of the DLPFC-thalamus connectivity in the modulation of pain. This study explored the influence of atDCS over M1 and DLPFC on central sensitization induced by low-frequency electrical stimulation (LFS).

Subjects were 39, right-handed, healthy individuals, ages 18 to 51 years. Sensations related to DCS were measured with the Noninvasive Brain Stimulation Questionnaire (NiBSQ). Using a 10-point visual analog pain scale (VAS), subjects received electrical stimulation to the right forearm, with stimulus intensity increased until the subject rated the pain at 5/10 on the VAS. Central sensitization was induced by repetitive low-frequency stimulation (LFS; 1Hz and 0.5 ms duration). Then, in separate sessions, anodal tDCS was applied (20 minutes, 1 mA) at left M1 alone, DLPFC alone, M1 and DLPFC simultaneously (M1+DLPFC), or sham.

Anodal tDCS at M1 increased the current level needed to evoke moderate pain compared to sham (p<0.001). This was not true of atDCS over DLPFC or M1+DLPFC. Anodal tDCS at the DLPFC reduced secondary hyperalgesia to levels below those of the sham condition. However, concurrent anodal tDCS over M1 and DLPFC did not reduce pain or hyperalgesia more than M1 alone or DLPFC alone.

Conclusion: This study found that a single session of anodal transcranial direct current stimulation at 1 mA for 20 minutes at the left motor cortex and the dorsolateral prefrontal cortex could modulate experimentally induced pain and secondary hyperalgesia.

Vo, L. et al. Anodal Transcranial Direct Current Stimulation Reduces Secondary Hyperalgesia Induced by Low-Frequency Electrical Stimulation in Healthy Volunteers. **J Pain.** 2022, February; 23 (2): 305-317.

EXERCISE TRAINING WITH BLOOD FLOW RESTRICTION

Resistance exercise with blood flow restriction (RE-BFR) has been found to increase the strength and muscle mass of elderly individuals. Aerobic exercise with BFR (AE-BFR) is thought to have additional benefits, including increased muscle mass, strength, and cardiorespiratory fitness. This study compared the cardiovascular responses to RE-BFR and AE-BFR.

Subjects had been physically inactive over the previous six months. All underwent graded exercise tests to determine their VO_2 peak. For each subject, a one-repetition maximum (1RM) was determined. In a crossover design, the subjects were exposed to each training protocol. The protocol for RE-BFR included 15

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repetitions plus 3 sets of 15 repetitions in a leg press machine, at 30% of 1RM and 50% BFR, with 1 min interval between sets. The protocol for AE-BFR involved 20-minutes of continuous exercise on the treadmill, at 40% of VO_2 peak at 50% BFR.

Compared to the AE-BFR group the RE-BFR group had higher systolic blood pressure, diastolic blood pressure the heart rate (HE), and peripheral vascular resistance ($p<0.001$ for all comparisons). Also, the HR was higher during recovery after RE-BFR than after AE-BFR. In addition, stroke volume and cardiac output increased more at the peak of AE-BFR as compared to RE-BFR ($p<0.001$ for both comparisons).

Conclusion: This study found that the exercise response to AE-BFR is relatively lower and less intense than that to exercise with RE-BFR.

Sardeli, A., et al. Cardiovascular Responses during and after Aerobic and Strength Exercises with Blood Flow Restriction in Older Adults. **Sci Sports**. 2022, February; 37(1): 76.e1-76.e5.

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