

# REHAB IN REVIEW

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## SELF-REPORTED HALLUCINATIONS IN OLDER ADULTS

Hallucinations have been reported among older adults with neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease. In these populations, ocular pathology has been identified as a risk factor for hallucinations. This study was designed to determine the association between visual impairment and hallucinations in the general population.

Data were analyzed from two longitudinal health surveys, the National Health and Aging Trends Study (NHATS) and the Health and Retirement Study (HRS). For this study, data of subjects 65 years of age or older were analyzed. Data collected included assessments of visual acuity, cognitive abilities, affective disorders, age, race and ethnicity, gender, smoking, level of education, annual household income, place of residence (e.g. nursing home), physical functional impairment and self-reported diagnoses of hypertension, diabetes, stroke, cataract surgery and hearing loss.

Data were included for 1,520 in the NHATS trial and 3,682 in the HRS trial. The prevalence of visual hallucinations ranged from eight percent among those 65 to 74 years of age to 60.6% among those over age 85. Hallucinations were associated with older age, female gender, race/ethnicity, hypertension, never smoking and hearing loss.

A history of stroke was more frequently reported by those with hallucinations (30.6% in the NHATS study and 39.5% in the HRS study). An increased odds ratio (OR) of hallucinations was noted among those with a self-reported inability to read a newspaper (OR 1.77), difficulty recognizing someone across the street (OR 2.48) and cataract surgery (OR 1.32-1.54).

**Conclusion:** This large, population-based study of the elderly U.S. population found that visual

dysfunction is associated with an increased likelihood of hallucinations.

Hamedani, A., et al. Self-Reported Vision and Hallucinations in Older Adults: Results from Two Longitudinal U.S. Health Surveys. *Age Aging*. 2020; 49: 843-849.

## MAXIMAL STRENGTH TRAINING FOR OSTEOPOROSIS IN HIV

The use of antiretroviral therapy to treat human immunodeficiency virus (HIV) has been shown to reduce bone mineral density (BMD). This study was designed to determine the effects of 12 weeks of maximal strength training on the BMD of patients living with HIV (PLHIV).

Subjects were adults, 18 to 45 years of age, each with HIV, and each having received ART for more than 12 months, with a documented reduced BMD. The participants were randomized to an exercise training group (TG) or to a control group (CG). The exercise group engaged in four sets of three to five repetitions at 85 to 95% of their one-repetition maximum (1 Rep Max). The 1 Rep Max was reevaluated every week to guide the progression of exercise intensity. Those in the control group were instructed to continue their usual lifestyle. Baseline and follow-up data included BMD, maximum strength, body weight, height, heart rate and body mass index.

Twenty-six participants were randomized, with 15 in the TG and 11 in the CG group. Compared to the CG, changes in BMD were significantly greater in the TG group for the lumbar spine ( $p=0.027$ ) and the femoral neck ( $p=0.006$ ). In addition, heart rate fell by 8.1 bpm in the TG and increased by 1.9 bpm in the CG ( $p=0.044$ ).

**Conclusion:** This study of patients living with HIV receiving antiretroviral therapy found that maximum strength training three times per week for 12 weeks could significantly improve bone mineral density.

Chisati, E., et al. Effects of Maximal Strength Training on Bone Mineral Density in People Living with HIV and Receiving Antiretroviral Therapy: A Pilot Study. *BMC Sports Sci Med Rehab*. 2020, October; 12: 67.

## KINESIO TAPE AND CERVICAL PROPRIOCEPTION FOR NECK PAIN

Among athletes with neck pain, proprioception has been shown to be impaired. This study evaluated the efficacy of kinesiotape (KT) as an intervention for athletes with mechanical neck pain (MNP).

Subjects were 66 athletes with MNP, referred for physical therapy. MNP was defined as pain of the cervical and shoulder region, aggravated by neck movements, sustained posture or palpation of the neck musculature. Cervical range of motion was measured, with pain intensity recorded on a visual analog scale (VAS) and functional neck disability assessed using the Neck Disability Index (NDI). Proprioception was calculated as cervical joint position errors in degrees as the subject was asked to actively reposition the head to a target position. After baseline assessment, the patients were randomized to a group using KT with appropriate tension or the same tape without tension (control). Outcomes were recorded before intervention (baseline), after placement and at three and seven days.

Sixty-six participants completed this study. Compared with the control group, position errors were significantly better in the KT group at seven days, when testing flexion, extension, left rotation and right rotation ( $p<0.001$  for all comparisons). Compared to the control group, the KT group also demonstrated a significantly greater reduction in VAS pain at seven days ( $p<0.001$ ). No significant difference was found between the groups in the NDI.

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**Conclusion:** This study of athletes with mechanical neck pain found that kinesiotape resulted in a significant improvement in joint position errors and pain.

Alahmari, K., et al. The Effect of Kinesio Taping on Cervical Proprioception in Athletes with Mechanical Neck Pain: A Placebo-Controlled Trial. **BMC Musculoskel Disord.** 2020; 21: 648.

### **FECAL CALPROTECTIN AND INFLAMMATION IN AXIAL SPONDYLOARTHRITIS**

The most common articular manifestations of axial spondylarthritis (axSpA) are axial symptoms such as chronic back pain and stiffness. Emerging evidence suggests that subclinical gut inflammation plays a role in the pathogenesis of this disease. As fecal calprotectin (FP) is a biomarker of gut inflammation, this study investigated factors associated with increased FP levels in patients with axSpA.

Consecutive patients seen with axSpA at one Korean hospital were recruited to the study. Stool samples were obtained to measure FP levels, with additional data including serum levels to determine erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level. Measures of disease activity included the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Ankylosing Spondylitis Disease Activity Score (ASDAS). Radiographs of the cervical spine, lumbar spine and pelvis were obtained at the time of FP measurement.

Among the 190 patients, 18% had increased FP levels. Compared to those without increased FP levels, those with increased FP levels had more peripheral symptoms and higher ASDAS-ESR, ESR and CRP. The levels of FP increased with disease activity ( $p = 0.002$ ).

**Conclusion:** This study of patients with axial spondylarthritis found that a measure of inflammation, fecal calprotectin, is significantly associated with disease activity.

Kang, K., et al. Relationship between Faecal Calprotectin and Inflammation in Peripheral Joints and Enteses in Axial Spondyloarthritis. **Scand J Rheumatol.** 2020; 40(5): 397-404.

### **GUT MICROBIOME AND COGNITIVE IMPAIRMENT IN ISCHEMIC STROKE**

Post-stroke cognitive impairment (PSCI) is a common complication. As recent studies have demonstrated that fecal microbial diversity differs between patients with Alzheimer's disease (AD) and healthy controls, this study investigated the gut microbiota (GM) composition in PSCI patients and its association with cognitive test scores and risk factors for PSCI.

Subjects were patients with ischemic strokes, 40 to 90 years of age, with no pre-existing history of dementia. All were assessed with the Montréal Cognitive Assessment (MoCA) three months post-stroke. Data collected included demographics, past medical history and stool samples for GM analysis. These data were reviewed to determine the risk factors for PSCI and the representative microbiota associated with PSCI.

An adjusted analysis revealed a significant relationship between PSCI and the abundance of *Enterobacteriaceae* ( $p=0.035$ ). Receiver operating characteristic (ROC) models, based upon the characteristic GM, indicated that the volume of *Enterobacteriaceae* could distinguish PSCI patients from those without cognitive impairment.

**Conclusion:** This study of patients with a recent ischemic stroke found that the gut bacteria, *Enterobacteriaceae* are highly increased in those with post-stroke cognitive impairment.

Ling, Y., et al. Gut Microbiome Signatures Are Biomarkers for Cognitive Impairment in Patients with Ischemic Stroke. **Front Aging Neurosci.** 2020, October: <https://doi.org/10.3389/fnagi.2020.511562>

### **NEUROPSYCHOLOGICAL PROFILE IN EARLY COGNITIVE DECLINE**

Cognitive decline among aging individuals is of increasing importance as the number of older adults continues to grow worldwide. As cognitive reserve is thought to insulate against cognitive decline through aging, this study assessed the association between comprehensive cognitive reserve and the neuropsychological profile.

This prospective study recruited individuals with subjective cognitive decline (SCD) or mild cognitive

impairment (MCI). All participants underwent psychiatric and a comprehensive neuropsychological evaluation. Cognitive reserve was evaluated using the Cognitive Reserve Index Questionnaire (CRIQ), which measured years of education (CRI-Education) and working activity (CRI-Working activity). Working activities were placed into five categories, depending upon the cognitive load required and time spent in the job. Leisure time (CRI-Leisure time), which assessed the type and frequency of cognitive leisure activities such as reading books, was also assessed, and a total score (CRI-Total) was determined.

Data were completed for 55 patients with an average age of 74 years, with 36 in the SCD group and 19 in the MCI group. Mini-Mental Status Exam scores were significantly related to CRI-Total ( $p=0.005$ ), as well as CRI Education ( $p=0.002$ ) and CRI-Leisure time ( $p=0.015$ ). Among CRI subscores, CRI-Leisure time directly affected the composite cognitive score ( $p=0.011$ ). CRI-Leisure activity was predictive of cognitive subdomains including language function ( $p=0.021$ ), memory ( $p=0.009$ ), visuospatial function ( $p=0.019$ ) and frontal executive function ( $p=0.041$ ), while CRI-Working activity predicted visuospatial function ( $p=0.015$ ).

**Conclusion:** This study of patients with subjective memory loss or mild cognitive impairment found that cognitive reserve is associated with global cognitive function. Only the subset of leisure activity was associated with naming ability and the composite cognitive score in the early stage of cognitive decline.

Lee, S., et al. Cognitive Reserve, Leisure Activity and Neuropsychological Profile in the Early Stage of Cognitive Decline. *Front Aging Neurosci.* 2020; October: 12.

### SERUM KYNURENINES AND POST-STROKE DEPRESSION

Post-stroke depression is observed in 30% to 50% of patients and is related to increased morbidity, mortality and poor functional prognosis. As the kynurenine pathway has been identified as important in the origin of depression, this study was designed to understand the association of kynurenine levels with symptoms of

anxiety/depression and disability in patients with subacute stroke.

This cross-sectional investigation included patients with a stroke, one to twelve months prior to study onset. Blood levels were obtained in order to measure levels of Tryptophan (Trp), L-kynurenine (L-Kyn) and kynurenic acid (KYNA). These levels were compared with clinical data.

Subjects were 60 patients with an average age of 57.3 years and a mean time since stroke of 5.2 months. Of these, 63% had significant depressive symptoms, as measured by the HADS-D. Depressed patients showed significantly higher levels of 3HK ( $p = 0.048$ ) and KYNA ( $p = 0.0271$ ) than did nondepressed patients. In addition, the 3HK levels were inversely correlated with functional scales: Barthel index ( $p = 0.02$ ), FIM ( $p = 0.01$ ).

**Conclusion:** This study found that plasma levels of 3HK and KYNA are correlated with the severity of depressive symptoms among patients with a recent stroke.

Carrilo-Mora, P., et al. Serum Kynurenines Correlate with Depressive Symptoms and Disability in Post-Stroke Patients: A Cross-Sectional Study. *Neurorehab Neural Repair.* 2020; 34(10): 936-944.

### TRANSIENT ISCHEMIC ATTACK WITHOUT SELF-AWARENESS

Due to their short-lasting nature, transient ischemic attacks (TIAs) can be overlooked by patients who are unaware of their symptoms, unless these are witnessed by others. This study was designed to understand the frequency and characteristics of patients with TIA, but no self-awareness, using data from the Prospective Multicenter Registry to Identify Subsequent Cardiovascular Events after Transient Ischemic Attack (PROMISE-TIA) study.

The PROMISE-TIA study was a multicenter, prospective, observational study of patients with a clinical diagnosis of TIA, who arrived within seven days of onset. Data included clinical information, premorbid functional status, as estimated with the modified Rankin scale (mRS) and questionnaires for the patient and bystanders regarding neurologic symptoms. The participants were classified as having no self-awareness (SA-) of their symptoms and self-awareness (SA+). Vascular lesions were defined as

stenosis of 50% or greater as detected by any modality.

Data were reviewed for 837 SA+ and 59 SA- patients. Those in the S-group were more often female ( $p=0.001$ ), older ( $p<0.001$ ), had a previous history of stroke ( $p<0.001$ ), had a premorbid disability ( $p<0.001$ ) and had atrial fibrillation ( $p<0.001$ ). Patients in the SA- group were more likely to have speech difficulty ( $p<0.001$ ) and less likely to have a sensory disorder than were those in the SA+ group ( $p<0.001$ ). Those in the SA- group arrived earlier and earned higher ABCD<sup>2</sup> scores.

**Conclusion:** This study, using data from the PROMISE-TIA trial, found that, among patients with a transient ischemic attack who arrived at stroke centers, 6.6% were unaware of their symptoms, having had these witnessed by bystanders.

Tanaka, K., et al. Transient Ischemic Attack without Self-Awareness of Symptoms Witnessed by Bystanders: Analysis of the PROMISE-TIA Registry. *Eur J Neurol.* 2020. Early view. <https://doi.org/10.1111/ene.14550>.

### INTRANASAL INSULIN FOR MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

Insulin, while best known for its role in peripheral glucose homeostasis, has been shown to cross the blood brain barrier and protect against the toxic effects of amyloid beta (AB) peptide. This study assessed the efficacy of intranasal insulin on cognition and Alzheimer's disease (AD) biomarkers.

Subjects were 55 to 85 years of age, diagnosed with amnesic mild cognitive impairment (MCI) or AD, with 121 randomized to receive 40IU/day of intranasal insulin (insulin arm), and 119 randomized to receive a daily placebo (placebo arm) for 12 months. Two different delivery devices were used for the intranasal insulin. This was followed by a six-month, open-label extension phase. The primary outcome variable was the change in score on the Alzheimer's Disease Activity Scale-Cognition (ADAS-cog-12), administered at baseline and at three-month intervals.

Cerebral spinal fluid and blood were collected to measure the AD biomarkers, A $\beta$ 42 and A $\beta$ 40, total tau protein and tau phosphorylated at threonine 181 (tau p-181). In addition, non-fasting blood samples were collected to assess glucose and

hemoglobin A1c. Baseline and follow-up MRIs were compared.

No significant difference was noted between treatment groups in changes in ADAS-cog-12 scores or in changes in clinical or cerebral spinal fluid outcomes. No significant adverse events were associated with treatment. In a secondary analysis of those using device 1, an advantage for the insulin arm on the ADAS-cog-12 was observed at the 12-month point, as were improved profiles for the CSF biomarker ratios of A $\beta$ 42 to A $\beta$ 40 and A $\beta$ 42 to total tau protein.

**Conclusion:** This study of patients with mild cognitive impairment or Alzheimer's disease found no cognitive or functional benefits of intranasal insulin treatment over 12 months.

Craft, S., et al. Safety, Efficacy, and Feasibility of Intranasal Insulin for the Treatment of Mild Cognitive Impairment and Alzheimer's Disease Dementia. A Randomized, Clinical Trial. **JAMA Neurol.** 2020, September; 77(9): 1099-1109.

#### **TICAGRELOR AND ASPIRIN OR ASPIRIN ALONE IN ACUTE ISCHEMIC STROKE OR TIA**

Among patients with an acute ischemic stroke or transient ischemic attack (TIA), the risk of a subsequent ischemic stroke is five to ten percent in the first few months. The Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA (acetylsalicylic acid) for Prevention of Stroke and Death (THALES) trial explored whether a 30-day treatment with ticagrelor and aspirin is superior to aspirin alone for the treatment of acute, non-cardioembolic, cerebral ischemia.

This multicenter, randomized, double-blind, placebo-controlled trial was completed at 414 sites in 28 countries. Subjects were 40 years of age or older with a mild to moderate, acute, non-cardioembolic, ischemic stroke, or a high risk transient ischemic attack (TIA), with a score of six or higher on the ABCD<sup>2</sup> scale. Those randomized to an ASA group received a loading dose of 300 to 325 milligrams of ASA, followed by daily doses of 75 to 100 mg. The combination group received ASA plus a loading dose of 180 mg of ticagrelor, followed by 90 mg twice per day. The primary outcome variable was a composite of stroke or death through 30 days of follow-up. Severe bleeding events were recorded.

Of the 11,016 patients who underwent randomization, a primary outcome event occurred in 5.5% of the combination group and 6.6% of the ASA group ( $p=0.02$ ). A subsequent ischemic stroke occurred in five percent of the combination group and 6.3% of the ASA group ( $p=0.004$ ). Severe bleeding occurred in 0.5% of the combination group and 0.1% of the ASA group ( $p=0.001$ ), with intracranial hemorrhage occurring in 0.4% of the combination group and 0.1% of the ASA group ( $p=0.005$ ).

**Conclusion:** This study of patients with mild to moderate, acute, non-cardioembolic, ischemic stroke or transient ischemic attack found a lower risk of a composite of stroke or death within 30 days among those who received ticagrelor and aspirin, as compared to those who received aspirin alone.

Johnston S., et al. Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA. **N Engl J Med.** 2020, July; 383: 207-217.

#### **EDOXYBAN IN THE VERY ELDERLY WITH ATRIAL FIBRILLATION**

Clinical guidelines for the prevention of stroke among patients with atrial fibrillation (AF) include the use of direct oral anticoagulants. However, many physicians are reluctant to prescribe these medications to very elderly patients due to perceived risks of bleeding. This study, the Edoxaban Low-Dose for Eldercare Atrial Fibrillation Patients (Eldercare-AF) trial assessed the effect of low-dose edoxaban for patients 80 years of age or older with nonvalvular AF.

This phase III, Japanese, multicenter, randomized study included patients 80 years of age or older with a history of nonvalvular AF, each of whom had CHADS<sub>2</sub> scores of two or higher and were thought to be inappropriate candidates for oral anticoagulants. The subjects were randomized to receive either a placebo or edoxaban, 15 mg once daily. The primary efficacy endpoint was the composite of stroke or systemic embolism. The primary safety endpoint was major bleeding.

Subjects were 984 patients with a mean age of 86.6 years, a mean body weight of 50.6 kg and a mean creatinine clearance of 36.3 ml/m. In the intention to treat sample, 15 patients in the edoxaban group and 44 in the placebo group had a stroke

or systemic embolism ( $p<0.001$ ). Twenty episodes of major bleeding occurred in the edoxaban group and 11 in the placebo group ( $p=0.09$ ). Gastrointestinal bleeding occurred in 14 patients in the treatment group and five in the placebo group (Hazard Ratio 2.85).

**Conclusion:** This study of elderly Japanese patients with nonvalvular atrial fibrillation found that a once daily 50 mg dose of edoxaban is superior to placebo in preventing stroke or systemic embolism, without a significantly elevated risk of major bleeding.

Okumura, K., et al. Low-Dose Edoxaban in Very Elderly Patients with Atrial Fibrillation. **N Engl J Med.** 2020, October 29; 383: 1735-1745.

#### **NERVE CONDUCTION STUDIES AND DEXTERITY IN CARPAL TUNNEL SYNDROME**

Individuals with carpal tunnel syndrome (CTS) frequently report reduced performance at work and in activities of daily living. As dexterity can be impaired by CTS, this study compared the results of the nerve conduction study (NCS) with those of a dexterity evaluation among patients presenting with symptoms of CTS.

Patients referred for a NCS were consecutively screened for eligibility for study participation. Those with suspected CTS, actively employed and 20 to 69 years of age were considered eligible. CTS severity was classified based on NCS results. The functional dexterity test (FDT), the Phalen test and the Tinel test were administered by a physical therapist held blind to the results of the electrodiagnostic study.

Subjects were 141 patients of whom 39 had bilateral symptoms, providing a sample of 180 hands. A significant relationship was found between FDT scores and NCS findings ( $p=0.001$ ). The FDT successfully discriminated subjects with severe/extreme NCS findings, with two thresholds identified. With the FDT added to the provocative tests, diagnostic accuracy improved, with a specificity of 0.97.

**Conclusion:** This study of patients presenting with symptoms of carpal tunnel syndrome found a strong, positive relationship between nerve conduction study results and functional dexterity.

Sartorio, F., et al. Relationship between Nerve Conduction Studies and the Functional Dexterity Test in

Workers with Carpal Tunnel Syndrome. **BMC Musculoskeletal Disord.** 2020; 21:679.

### ULTRA-HIGH-FREQUENCY ULTRASOUND

With the recent development of ultra-high-frequency ultrasound (UHF-US), a significantly better visualization of nerve anatomy is now possible. This study compared sural nerve UHF-US evaluation to histopathologic findings in patients with polyneuropathies.

Subjects were patients with severe, progressive neuropathies, presenting to the Peripheral Nervous System Muscle Center of the Nice University Hospital, Nice, Italy. All subjects underwent electrodiagnostic evaluation of motor and sensory nerves bilaterally. UHF-US evaluation was performed on the sural nerve, which was then biopsied for histological analysis. Results of those two evaluations were compared.

Ten patients with severe, progressive neuropathies were enrolled in the study. Sural nerves were easily identified by UHF-US. An inflammatory infiltrate was found in five patients. All nerves with an inflammatory infiltrate on biopsy had a hyperechogenicity appearance on UHF-US ( $p < 0.03$ ). Nerve fascicles were easily identified by UHF-US.

**Conclusion:** This study of patients with severe progressive neuropathies found that ultra-high frequency ultrasound findings of hyper-echogenicity were significantly related to nerve inflammation.

Puma, A., et al. Ultra-high Frequency Ultrasound Imaging of Sural Nerve: A Comparative Study with Nerve Biopsy and in Progressive Neuropathies. **Musc Nerve.** 2020, Early View. doi: 10.1002/mus.27073

### TRANSCUTANEOUS VAGUS NERVE STIMULATION FOR RHEUMATOID ARTHRITIS

Previous studies have suggested that the vagus nerve, through the cholinergic anti-inflammatory pathway, can suppress the production of pro-inflammatory cytokines, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ). As TNF- $\alpha$  is a central pathophysiologic mediator of rheumatoid arthritis (RA), this study investigated the effects of short-term, noninvasive vagus nerve stimulation

(nVNS) on disease activity and pro-inflammatory cytokines in patients with RA.

This proof of concept study included patients with RA who underwent non-invasive evaluation of autonomic measures, including cardiac vagal tone (CVT) and venous blood sampling for cytokines. A nVNS device was a set to deliver 120 seconds of n-VNS, with stimulation three times per day. The main outcome measures were change in resting CVT, Disease Activity Scores, based on 28-joint count-C-reactive protein (DAS28-CRP) and cytokines, at baseline and after four days of treatment.

Subjects were sixteen participants with active RA (DAS28 $>3.2$ ) and 20 with RA but low disease activity (DAS28 $<2.6$ ). Among those with active RA, nVNS resulted in small, but significant, reductions in DAS28-CRP ( $p=0.02$ ), CRP ( $p=0.001$ ) and cytokine IFN- $\gamma$  ( $p = 0.02$ ). Such effects were not seen in those with low disease activity. The n-VNS was not associated with any change in CVT, HR or diastolic BP across the study period, although there was a 12 -mmHg reduction in systolic BP ( $p = 0.003$ ).

**Conclusion:** This study of patients with rheumatoid arthritis found that noninvasive vagus nerve stimulation can result in anti-inflammatory effects and reduce symptoms.

Drewes, A., et al. Short-Term, Transcutaneous, Non-invasive Vagus Nerve Stimulation may Reduce Disease Activity and Pro-Inflammatory Cytokines in Rheumatoid Arthritis: Results of a Pilot Study. **Scand J Rheumatol.** 2020; <https://doi.org/10.1080/03009742.2020.1764617>.

### CORTICOTROPIN AND RHEUMATOID ARTHRITIS

Melanocortin Receptor (MCR) agonists have anti-inflammatory and immune modulating properties mediated by receptors expressed on cells relevant to arthritis. This animal study evaluated the efficacy of an MCR agonist, repository corticotropin injection (RCI), for reducing the effects of a laboratory induced arthritis.

Using a rat collagen-induced arthritis (CIA) model, disease induction was performed. On day 13, the animals were randomized to receive subcutaneous RCI (40 U/kg,

160 U/kg or 400 U/kg, twice daily) alone or in combination with etanercept (ENT), 10 mg/kg three times daily, ENT alone or vehicle alone (placebo). The treatments were initiated on day 13 and continued through day 19. Arthritis disease was represented as an increase in ankle diameter. On day 20, the animals were sacrificed for histopathologic assessment.

Compared to the placebo group, all intervention groups demonstrated significantly greater decreases in ankle diameter ( $p < 0.05$ ). Compared with ENT alone, RCI 160 or 400 U/Kg further reduced ankle diameter. Microscopic examination of the diseased paws revealed destructive polyarthritis, characterized by synovial and periarticular edema, mixed inflammatory cell infiltration, cartilage damage and bone resorption. As compared with controls, measures of inflammation were reduced in the ENT group, including RCI 160 U/kg, RCI 400 U/kg, ENT+RCI 160 U/kg and ENT +RCI 400 U/kg by nine percent, 19%, 26%, 29% and 55%, respectively. Also as compared with controls, cartilage damage was reduced by 22% in the ENT group ( $p < 0.05$ ) and by 51% in the ENT+ RCI 400 U/kg group ( $p < 0.0001$ ).

**Conclusion:** This animal study found that corticotropin, as an adjunct therapy with etanercept, reduced structural damage in an experimental model of rheumatoid arthritis.

Decker, D., et al. Repository Corticotropin Injection Attenuates Collagen-Induced Arthritic Joint Structural Damage and Has Enhanced Effects in Combination with Etanercept. **BMC Musculoskeletal Disord.** 2020; 21: 586.

### FRESH FROZEN MENISCAL ALLOGRAFT TRANSPLANT OUTCOMES

Meniscal allograft transplant (MAT) is designed to reduce pain in patients with post-menisectomy syndrome. As most previous studies have been limited to short-term outcomes, this study evaluated the ten-year clinical outcomes of patients treated with this procedure.

Data were reviewed for 175, consecutive MAT procedures, performed between June of 2006 and March of 2013. Indications for the procedure were pain due to a previous total or subtotal menisectomy, with osteoarthritis

grade I through III according to the Kelgrin-Lawrence scale. Those with anterior-posterior knee laxity underwent anterior cruciate ligament (ACL) reconstruction, and those with chondral lesions smaller than 2 cm<sup>2</sup> underwent microfracture procedures. Preoperatively, patients were evaluated with Lysholm scores, the Tegner Activity Scale, and a zero to 100 visual analog scale (VAS) for pain. At 10-year follow-up, these measures were repeated, with the addition of the Knee Injury and Osteoarthritis Outcome Score (KOOS) subscale.

A complete 10-year follow-up was available for 38 patients. Rates of survival, free from surgery, were 91% at five years and 86% at 10 years. Excluding those who experienced surgical failure with graft removal, and using the Lysholm scores for outcomes, 36% were rated as excellent, 21% as good, 31% as fair and 12% as poor. At final follow-up, 75% of the patients reported involvement in sports activity, mostly low-impact.

**Conclusion:** This 10-year follow-up of patients undergoing meniscal allograft transplant surgery found that, at 10 years, 70% demonstrated satisfactory clinical outcomes.

Grassi, A., et al. Long-Term Outcomes and Survivorship of Fresh Frozen Meniscal Allograft Transplant with Soft Tissue Fixation. Minimum 10-Year Follow-Up Study. *Am J Sports Med.* 2020, August; 48(10): 2360-2369.

### IMPROVEMENT OF ROTATOR CUFF TEARS: SURGICAL VERSUS NONSURGICAL

The prevalence of rotator cuff tears increases with age and will likely continue with the aging of the U.S. population. However, sparse evidence is available to guide clinical decision making when providing treatment options for these patients. This study compared the time to achieve clinically meaningful improvement in patients with rotator cuff tears treated surgically versus those treated conservatively.

The Rotator Cuff Outcomes Work Group (ROW) is a multicenter, longitudinal, cohort study including patients diagnosed with symptomatic partial or full rotator cuff tears. The treatment decision was established between the patient and the physician, with shared decision-making. Shoulder pain and function outcomes were measured using the Shoulder Pain and Disability Index (SPADI) and the American Shoulder

and Elbow Surgeons (ASES) Standardized Shoulder form. Patients were followed for up to 60 months in order to determine the time to achieve the minimally clinically important difference (MCID) in improvement in the SPADI and the ASES scores.

The time to achieve at least a 30% reduction in SPADI scores favored the non-operative group, reaching the maximum difference at 3.25 months. The time to achieve at least a 50% reduction in SPADI scores favored the surgical group, with the maximum difference at 15.5 months. A similar pattern was seen for the ASES scores.

**Conclusion:** This study of patients with rotator cuff tears found that those treated non-surgically improved more quickly than did the surgical group, with the surgical group achieving better long-term results.

Song, A., et al. Comparative Time to Improvement in Nonoperative and Operative Treatment of Rotator Cuff Tears. *J Bone Joint Surg.* 2020, July; 102(13): 1142-1150.

### OPEN VERSUS MINIMALLY INVASIVE DECOMPRESSION FOR SPONDYLOLISTHESIS

Degenerative lumbar spondylolisthesis is one of the most common causes of low back pain. For those who fail conservative treatment, open laminectomy is a common intervention, although complicated by well-recognized drawbacks. Minimally invasive surgery (MIS) has been introduced to reduce the trauma of surgical intervention. This study compared the outcome of conventional open techniques with that of MIS techniques for patients with grade I spondylolisthesis.

The Quality Outcomes Database was queried for patients undergoing surgery for grade I degenerative lumbar spondylolisthesis between July 1, 2014, and June 30, 2016. This database was established to evaluate risk adjusted expected morbidity, 30-day clinical outcomes of interest and 12-month patient-reported outcomes (PROs)

Data were included for 608 patients undergoing surgery across 12 sites, of whom 140 underwent decompression alone. Of these, 71 underwent an MIS decompression and 69 underwent open decompression. Patients undergoing MIS decompression had a length of stay of 0.68 days, compared to 1.83 days for those undergoing open

decompression (p<0.001). Complications occurred in 1.4% of the MIS group and 7.2% of the open group (p=0.11). A multivariable analysis revealed that open surgery resulted in higher patient satisfaction at two years than did MIS (p=0.0005).

**Conclusion:** This study of patients with grade I spondylolisthesis found that both open and MIS procedures significantly improved back and leg pain and quality of life.

Bisson, E., et al. Open versus Minimally Invasive Decompression for Low-Grade Spondylolisthesis: Analysis from the Quality Outcomes Database. *J Neurosurg Spine.* 2020; 33(3): 349-359.

### PERSISTENT CONCUSSIVE SYMPTOMS AND EXERCISE

The estimated rate of concussion in the pediatric population is 600 per 100,000, with 20%-30% experiencing post-concussive symptoms one month after injury. This study assessed the effectiveness of an exercise-based intervention in the pediatric population with post-concussive symptoms at one-month post-injury.

This multicenter, prospective study included patients eight to 17 years of age with a concussion and a symptom of post-concussion syndrome at least once per week. The subjects were randomized to an active rehabilitation group (n=36) or a control group (n=13) who received standard care. The active rehabilitation intervention involved aerobic activity, sport specific activity, mental imagery, education and a home program. Standard care comprised rest/light symptom-limited activities, academic adaptations and restriction from physical activities until symptom resolution. Outcomes were measured at three time periods over six weeks. The primary outcome measure was the Post-Concussion Symptom Inventory (PCSI).

The PCSI scores decreased over time for both the control and intervention groups (p=0.01), with no significant differences between the groups (p=0.33). Compared to the control group, the intervention group obtained higher scores in quality of life (p=0.04), reduced anger (p=0.02), improvements with tandem gait (p=0.07) and reduced fatigue (p=0.09).

**Conclusion:** This study of young patients with post-concussive symptoms found that an active intervention was as effective as standard care in reducing post-concussive symptoms but resulted in

greater quality of life and reduced anger and fatigue.

Gauvin-Lepage, J., et al. Effectiveness of an Exercise-Based, Active Rehabilitation Intervention for Youth Who are Slow to Recover after Concussion. *Clin J Sports Med*. 2020 Sep; 30(5): 423-432.

### PLASMA ACE2 AND RISK OF DEATH

The renin-angiotensin system is a hormonal cascade resulting in several effective cardiovascular disease therapeutics. Within this system, angiotensin-converting enzyme (ACE) cleaves angiotensin I to angiotensin II, acting on the type I angiotensin II receptor. As recent evidence has shed light on an important counterbalancing component of the renin-angiotensin system axis, through the action of ACE2, this study reviewed the association between ACE2 levels and cardiovascular events.

Data were obtained from the Prospective Urban Referral Epidemiology (PURE) study, with data from 14 countries in five continents. All subjects underwent measures of plasma concentrations of ACE2 and were followed for outcomes of interest, including death, myocardial infarction, stroke, heart failure and diabetes. Medication use was documented to determine whether anti-hypertensive therapies (ACE inhibitors, calcium channel blockers and  $\beta$  blockers) had an influence on circulating ACE2 levels.

Data were included for 10,753 adults, with assessment of traditional cardiovascular risk factors, as well as plasma levels of ACE2. After adjusting for demographic variables and clinical risk factors, increased ACE2 levels were found to be associated with a higher risk for overall death (HR 1.35 per standard deviation), cardiovascular death (HR 1.4 per standard deviation), non-cardiovascular death (HR 1.34 per standard deviation), heart failure (HR 1.27 per standard deviation), myocardial infarction (HR 1.23 per standard deviation), stroke (HR 1.21 per standard deviation), and diabetes (HR 1.44 per standard deviation). Compared with known clinical risk factors, ACE2 was the highest ranked variable for predicting total deaths, cardiovascular and non-cardiovascular deaths ( $p < 0.0001$  for all comparisons).

**Conclusion:** This international study of community-based adults found that high levels of plasma ACE2 are associated with greater

risks of death, stroke, myocardial infarction, diabetes and heart failure, independent of traditional cardiac risk factors.

Narula, S., et al. Plasma ACE2 and Risk of Death or Cardiometabolic Diseases: A Case-Cohort Analysis. *Lancet*. 2020, October 3; 396: 968-976.

### PREHABILITATION BEFORE ELECTIVE CORONARY ARTERY BYPASS GRAFT SURGERY

Approximately 60% of all coronary artery bypass graft (CABG) surgeries involved patients 65 to 80 years of age. As a poor physical health status prior to heart surgery is associated with longer hospitalization, interventions to counteract this problem have received increased attention. This study evaluated the effects of a two-week prehabilitation program on patients awaiting elective CABG surgery.

This single center, randomized, controlled trial invited patients with stable coronary artery disease. The subjects were randomized to a control group or an intervention group, to participate in a two-week exercise program, including individualized, supervised cycle ergometry training three times a week at 70% of peak oxygen uptake. The aerobic sessions were gradually increased to two, 25-minute cycling sessions, with a 15-minute session of light gymnastics separating these.

Data were included for 171 subjects. Comparing baseline to two-week follow-up, greater improvement was noted in the treatment group than in the control group on the Six Minute Walk Distance (6MWD) and Timed Up and Go (TUG) tests ( $p < 0.001$  for both). No adverse effects were noted. Similar effects were noted post-operatively, with better improvement in the intervention group on the 6MWD ( $p < 0.001$ ), the TUG ( $p = 0.003$ ) and measures of quality of life ( $p < 0.001$ ).

**Conclusion:** This study of patients awaiting CABG surgery found that a two-week exercise program improved postoperative functional capacity.

Steinmetz, C., et al. Prehabilitation in Patients Awaiting Elective Coronary Artery Bypass Graft Surgery-Effects on Functional Capacity and Quality of Life: A Randomized, Controlled Trial. *Clin Rehab*. 2020; 34(10): 1256-1267.

### MORTALITY AND MUSCULOSKELETAL PAIN

According to the World Health Organization's Global Burden of Disease study in 2017, low back pain is a leading cause of years lived with disability (YLD). This study explored the relationship between musculoskeletal pain and mortality.

Data were obtained from the National Institute of Public Health in Denmark, a nationally representative survey of the citizens 16 years of age or older. A randomly selected group was asked about musculoskeletal conditions. Variables included musculoskeletal pain within the prior 14 days, with further questions regarding pain location and severity. These data were compared to all-cause mortality and the cause of death.

Data were available for 4,817 persons, with a mean follow-up of 19.1 years. Of these, 41% had experienced musculoskeletal pain within the prior 14 days. All-cause mortality rates increased with increased musculoskeletal pain severity and increased spread of musculoskeletal pain. The risk was greatest for men with strong pain (Hazard Ratio (HR) 1.66) and women with widespread pain (HR 1.49).

**Conclusion:** This Danish study found a higher risk of mortality among those with musculoskeletal pain.

Holmberg, T., et al. Mortality among Persons Experiencing Musculoskeletal Pain: A Prospective Study among Danish Men and Women. *BMC Musculoskelet Disord*. 2020, October 8; 21(1): 666.

### ATOGEPAANT FOR EPISODIC MIGRAINES

Globally, migraine is ranked as the second leading cause of years lived with disability. As increasing concentrations of calcitonin gene related peptide (CGRP) have been found in patients with migraine attacks, studies have reviewed the effectiveness of CGRP receptor antagonist as an acute treatment of migraine. This study assessed the efficacy of atogepant, a CGRP receptor antagonist with a half-life of 10 hours.

This multicenter, randomized, double-blind, placebo-controlled trial included patients 18 to 75 years of age with a history of migraine. The subjects were randomized to receive a placebo, atogepant, 10 mg once daily, atogepant, 30 mg once daily, atogepant, 60 mg once daily, atogepant, 30 mg twice per day or

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Tony Nguyen, M.D.  
Sami Strutner, M.D.  
Peter Lee, D.O.  
Univ. of California, Irvine, CA

\*Chloe McCloskey, M.D.  
Leah Bowlin, D.O.  
Alexander Ramirez, M.D.  
Univ. of Pennsylvania, Phila, PA

\*Austin Marcolina, D.O.  
Kegan J. Cuniff, M.D.  
Sarah Matthews, M.D.  
Veronica Reyor, D.O.  
Univ. of TX SW Med Ctr., Dallas, TX

\*Jacob Boomgaardt, M.D.  
Univ. of Virginia, Charlottesville, VA

\*Andrew Minkley, M.D.  
Lyndsey Booker, M.D.  
Brian Cervoni, M.D.  
Jami Montagnino, M.D.  
Univ. of Washington, Seattle, WA

\*Bonnie Weigert, M.D.  
Jonathan Liang, M.D.  
Simon Wallace, M.D.  
Univ. Of Wisconsin, Madison, WI

**Executive Editor Emeritus**  
Donald F. Langenbeck, Jr., M.D.

**Subscription Manager**  
Michael P. Burke, M.S.

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atogepant, 60 mg twice daily. The primary efficacy measure was the change from baseline in mean, monthly migraine days across the 12 weeks of the trial.

Compared with placebo, the change in mean, monthly migraine days was reduced in the groups receiving atogepant, 10 mg once daily ( $p=0.024$ ), atogepant, 30 mg once daily ( $p=0.039$ ), atogepant, 60 mg once daily ( $p=0.039$ ), atogepant, 30mg twice daily ( $p=0.0034$ ) or atogepant 60mg twice daily ( $p=0.0031$ ). A 50% or greater reduction in monthly migraine days was noted in significantly more (compared with placebo) of those in the 30mg BID ( $p=0.034$ ) group and in 62% of those receiving 60mg twice daily ( $p=0.0097$ ).

**Conclusion:** This study of patients with episodic migraine found atogepant to be effective in reducing the number of migraines experienced per month.

Goadsby, P., et al. Safety, Tolerability and Efficacy of Orally Administered Atogepant for the Prevention of Episodic Migraine in Adults: A Double-Blind, Randomised, Phase 2b/3 Trial. *Lancet Neurol.* 2020; 19: 727-737.

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