

# BONES & BRAIN

## IN REVIEW

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### RETATRUTIDE FOR OBESITY

Obesity treatment has evolved, with the introduction of potentially highly effective nutrient-stimulated hormone-based therapeutics. This study explores the efficacy of retatrutide, a medication that engages G-protein-coupled receptor targets, including glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP), for the achievement of meaningful weight reduction.

Subjects were 338 adults, 18 to 75 years of age, who were provided with diet and lifestyle counseling, and randomized to receive 48 weekly injections of a placebo or of retatrutide. The retatrutide dosing groups were, A) 1 mg, B) 4 mg with an initial dose of 2 mg, C) 4 mg with an initial dose of 4 mg, D) 8 mg with an initial dose of 2 mg, E) 8 mg with an initial dose of 4 mg, F) 12 mg with an initial dose of 2 mg. The primary endpoint was the percent change in body mass index (BMI) from baseline to 24 weeks.

The mean reductions in BMI at week 24 were 1.6% in the placebo group, 7.2% in group A, 11.8% in group B, 13.9% in group C, 16.7% in group D, 17.9% in group E, and 17.5% in group F. At 48 weeks, the changes in these same groups were 2.1%, 8.7%, 16.3%, 17.8%, 21.7%, 23.9%, and 24.2%, respectively. In addition, over the course of the study, several cardiometabolic measures improved, including systolic and diastolic blood pressure and levels of glycated hemoglobin, fasting glucose, insulin, and lipids (except HDL).

**Conclusion:** This phase two trial of patients with obesity, treated with weekly injections of an agonist targeting G-protein-coupled receptor targets found that the participants achieved a mean weight reduction of up to 24.2% after 48 weeks.

Jastreboff, A., et al. Triple Hormone Receptor Agonist, Retatrutide, for Obesity: A Phase Two Trial. *N Eng J Med.* 2023, Aug 10: 389: 514-526.

### SAFETY OF HIP REPLACEMENT FOR NONAGENERIANS

Most countries are experiencing rapid aging of their populations. A fast-growing group of the elderly are those over 90 years of age. This German study evaluated the safety of total hip arthroplasty (THA) among nonagenarians.

Data were obtained from the German Arthroplasty Registry (Endoprothesenregister Deutschland (EPRD)), using data collected from 2012 through 2021. Data were extracted from the records of patients 60 years of age or older who had undergone elective THA. The primary endpoints were major and minor complications, including mortality.

Of the 1,859 nonagenarians studied, major complications were noted in 19.9%. Among those younger, major complications were found in 10.7% of those 80-89 years of age, 6.2% of those 70- to 79 years of age and 3.7% of those 60-69 years of age. The most frequent major complications were acute renal failure, delirium, and coagulopathy.

**Conclusion:** This study of patients 90 years of age or older undergoing total hip arthroplasty found that major complications occur in almost 20%.

Leopold, V., et al. Is Elective Total Hip Arthroplasty Safe in Nonagenarians?: An Arthroplasty Registry Analysis. *J Bone Joint Surg.* 2023, October 18; 105 (20): 1583-1593.

### TAI CHI IN PARKINSON'S DISEASE

Parkinson's disease (PD) is a common debilitating and progressive neurodegenerative movement disorder. Studies that have focused on exercise training have shown a short-term benefit of tai chi (TC) for improving the symptoms of PD. This study assessed the long-term effects of TC on the motor and nonmotor symptoms of PD.

Subjects were patients diagnosed with PD, randomized to a control group (n=187) or a TC group (n=143). The TC training included home practice, twice per week for 60 minutes per session. The participants were evaluated at baseline and were followed with the Unified Parkinson's Disease Rating Scale (UPDRS), the Timed Up and Go Test (TUG), and measures of balance, anxiety, cognition, and affect. Cognitive function was assessed with the Parkinson's Disease Cognitive Rating Scale (PDCRS). The primary outcome variable was the rate of change on the UPDRS, and the rate of change in levodopa equivalent daily dosage (LEDD) per year.

At a mean of 4.3 years, worsening of UPDRS scores was significantly greater in the control group than in the TC group at all times measured (p<0.001). The TC group demonstrated continuous improvement in quality of life, as assessed with the Parkinson's Disease Questionnaire, sleep, as assessed with the Epworth Sleep Scale and the Parkinson's Disease Sleep Scale (ESS, PDSS), and cognition as assessed with the PDCRS.

**Conclusion:** This study of patients with Parkinson's disease found that tai chi, practiced for one hour, twice per week, can reduce motor and cognitive deterioration.

Li, G., et al. Effect of Long-Term Tai Chi Training on Parkinson's Disease: A 3.5-Year Follow-Up Cohort Study. *J Neurol Neurosurg Psychiatry.* 2023, October 24: 1-7. doi: 10.1136/jnnp-2022-330967.

### DOPAMINE TRANSPORTER BINDING IN PARKINSON'S DISEASE IS ASSOCIATED WITH APATHY AND ANHEDONIA

Apathy and anhedonia are disabling symptoms of Parkinson's disease (PD). A striatal dopaminergic deficit is thought to be central to

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motivational symptoms in PD but has never been studied longitudinally. Dopamine transporter (DAT) imaging is commonly used as a diagnostic tool, as it is sensitive to degeneration of dopaminergic nigrostriatal pathways. Given that apathy and depression are associated with lower striatal DAT specific binding ratio (SBR), this study examined the longitudinal relationship between striatal DAT SBR and the emergence and progression of apathy and anhedonia in PD.

This cohort study included 412 patients participating in the Parkinson's Progression Markers Initiative (PPMI) study of newly diagnosed PD patients. Apathy and anhedonia were assessed using a composite score derived from relevant items of the 15-item Geriatric Depression Scale (GDS-15) and part I of the MDS-Unified Parkinson's Disease Rating Scale. Dopaminergic degeneration was examined by DAT imaging, with the assessed in the bilateral caudate, putamen, and occipital cortex (reference tissue).

The longitudinal analysis revealed that the overall relationship between striatal DAT SBR and apathy/anhedonia across all time points was non-significant. A post hoc analysis revealed that, while striatal DAT SBR was not significantly associated with apathy/anhedonia at baseline ( $p=0.54$ ), this relationship emerged over follow-up ( $p<0.01$ ), strengthening as time progressed.

**Conclusion:** This study of patients with Parkinson's disease found a negative relationship between striatal DAT SBR and apathy/anhedonia symptoms at baseline, with an emergence of the relationship over time.

Costello, H., et al. Longitudinal Decline in Striatal Dopamine Transporter Binding in Parkinson's Disease: Associations with Apathy and Anhedonia. *J Neurol, Neurosurg, Psych.* 2023, Oct;94 (10):863-870.

#### **WIRELESS PATCH MONITORING C-REACTIVE PROTEIN**

Of the leading causes of death worldwide, the top three, ischemic heart disease, stroke, and chronic obstructive pulmonary disease (COPD) are characterized by chronic inflammation. As C-reactive protein (CRP) is associated with chronic inflammation, and studies have shown a strong correlation between

sweat and serum CRP levels, this study assessed the efficacy of a wireless wearable biosensor for monitoring CRP in the sweat.

The subjects were current or former smokers, with or without COPD, 40–80 years of age. All wore an autonomous iontophoresis module for on-demand and controlled sweat extraction; a sweat-gland-powered, skin-interfaced microfluidic module that capitalizes on sweat flow to achieve fully automated protein and detector antibody (dAb) capturing.

For comparison, the subjects wore a Macroduct collector, over a period of 60 min for sweat collection. To affirm the presence of CRP in sweat a proteomic assessment was made. The healthy participants were grouped according to smoking status (current, former, and never smokers), as well as by COPD and heart failure status.

The CRP levels in both serum and sweat were greater in current smokers compared with former and never smokers. Among patients with COPD, serum and sweat CRP values were greater in former smokers than current smokers, consistent with irreversible tissue damage. In patients with current active infections, a substantial increase (over tenfold on average) was found in both serum and sweat CRP compared with healthy participants.

**Conclusion:** This study found that wearable, autonomous wireless monitors could detect and quantify levels of C-reactive protein, indicating inflammation in the blood.

Tu, J., et al. A Wireless Patch for The Monitoring of C-reactive Protein in Sweat. *Nat Biomed Eng.* 2023, October; 7(10): 1293-1306.

#### **AUTOMATED ELECTROENCEPHALOGRAPHY USING ARTIFICIAL INTELLIGENCE**

Electroencephalography (EEG) is used in the diagnostic workup of patients with suspected epilepsy and other disorders of the brain. However, expertise in reading clinical EEGs is not widely available. This study was designed to develop and validate an artificial intelligence (AI) model to help distinguish abnormal from normal EEG readings.

Data were obtained from 30,493 EEG records of anonymous patients collected in Norway and Denmark. After an AI model (Standardized Computer-based Organized Reporting of EEG–Artificial

Intelligence [SCORE-AI]) was created, the EEGs underwent human expert assessments using SCORE terminology. The SCORE-AI was validated using three independent test data sets. These included a multicenter data set of 100 representative EEGs evaluated by 11 experts, a single-center data set of 9,785 EEGs evaluated by 14 experts, and a data set of 60 EEGs with an external reference standard. The outcome measure was the degree of agreement among the 11 experts, and between the experts and the artificial intelligence scores.

The scoring of the SCORE AI achieved high accuracy, with an area under the receiving operating characteristic curve between 0.89 and 0.96 for the different categories of EEG abnormalities. The overall accuracy of SCORE-AI (88.3%) was similar to that of the human experts (83.3%) and more accurate ( $p < 0.001$ ) than three previously published AI models.

**Conclusion:** This diagnostic study, using human experts as the gold standard, describes an artificial intelligence program capable of completing a fully automated and comprehensive clinically relevant assessment of routine EEGs.

Tveit, J., et al. Automated Interpretation of Clinical Electroencephalograms Using Artificial Intelligence. *JAMA Neurol.* 2023, Aug; 80(8): 805-812.

### GLOBAL EFFECT OF MODIFIABLE RISK FACTORS ON CARDIOVASCULAR DISEASE

Cardiovascular diseases are the most common noncommunicable conditions worldwide, accounting for one third of all diseases globally. The five modifiable risk factors associated with this disease are, body mass index (BMI), systolic blood pressure (SBP), low density lipoprotein cholesterol, tobacco smoking, and diabetes. This study used pooled data from cohort studies to estimate the contributions of each of these risk factors to the 10-year incidence of cardiovascular disease.

Data were pooled and harmonized from 112 cohort studies, including 1,518,028 participants in eight geographic regions. Five risk factors (BMI, SBP, non-HDL cholesterol, current smoking, and diabetes) and two outcomes (cardiovascular disease and death from any cause) were assessed. For

the risk factors, region and gender specific population attributable fractions were estimated for the 10-year incidence of cardiovascular disease.

The percent of the ten-year incidence of cardiovascular disease that could be attributed to these five risk factors combined, was 57.2% among women and 52.6% among men. For mortality, the corresponding values for 10-year, all-cause mortality were 22.2% for women and 19.1% for men. The prevalence and effect of these risk factors varied geographic region.

**Conclusion:** This study found that over 50% of the cases of cardiovascular disease can be attributed to five modifiable risk factors, with the effect of each of these varying by sex and geographic region.

The Global Cardiovascular Risk Consortium. Global Effect of Modifiable Risk Factors on Cardiovascular Disease and Mortality. *N Eng J Med.* 2023, October 5; 389 (14): 1273-1285.

### HEALTHY LIFESTYLE IN LATE LIFE, LONGEVITY GENES, AND LIFE EXPECTANCY

Individuals 65 years of age or older now account for 13.5% of the population of China. This study, the Chinese Longitudinal Healthy Longevity Survey (CLHL), explored the associations among adherence to a healthy lifestyle (HL), genetics, and all-cause mortality.

The CLHL is a population-based, prospective cohort study launched in 1998, with seven follow-up interviews conducted through 2018. From the CLHL, 36,164 subjects were included in the lifestyle analysis. An HL score was based on four factors associated with healthy longevity, including current non-smoking status, non-harmful alcohol consumption, being physically active, and following a healthy diet. From these, three lifestyle groups were formed, unhealthy (the bottom tertile of the weighted healthy lifestyle score), intermediate (middle tertile), and healthy lifestyle (top tertile). A genetic risk score was created for 9,633 subjects using 11 single nucleotide polymorphisms (SNPs) associated with longevity.

During the follow-up, as compared to those in the unhealthy lifestyle category, those in the healthy lifestyle group had significantly lower all-

cause mortality (Hazard Ratio, HR 0.56;  $p < 0.0001$ ). The adjusted HR of mortality risk of the high genetic risk group was 1.07 ( $p = 0.013$ ) compared with those in the low genetic risk group. When genetic risk and healthy lifestyle were combined, compared to those in the highest tertile of lifestyle and the lowest genetic risk, those in the bottom tertile of lifestyle and highest genetic risk had a higher rate of mortality (HR 1.80,  $p < 0.0001$ ).

**Conclusion:** This study found that, even late in life, a healthy lifestyle is associated with lower mortality risk and longer life expectancy.

Wang, J., et al. Healthy Lifestyle in Late Life, Longevity Genes, and Life Expectancy Among Older Adults: A 20-Year, Population Based, Prospective Cohort Study. *Lancet Healthy Longev.* 2023, October, 4(10) E535-E 543.

### THROMBECTOMY IN PEDIATRIC LARGE VESSEL OCCLUSION STROKE

Large vessel occlusion (LVO) stroke in pediatric patients is not well studied. Mechanical thrombectomy for pediatric patients with LVO has not been widely accepted due to a lack of clinical data. This study was designed to determine whether pediatric patients with LVO stroke can benefit from thrombectomy.

This case-control study included 31 patients <18 years of age, hospitalized with a stroke between January of 2011 and April of 2022. The patients were matched with patients who received medical therapy only. The primary outcome measure was the pediatric modified Rankin Scale (mRS).

Three months after the stroke, patients with LVO who underwent thrombectomy had better mRS scores than did the control group ( $p = 0.01$ ). Compared with controls, the absolute risk reduction for a poor outcome at three months was 19.2% for those undergoing thrombectomy. At final follow-up (33 months), compared to controls, patients undergoing thrombectomy were significantly more likely to have better mRS scores ( $p = 0.02$ ).

**Conclusion:** This study of patients under 18 years of age, with a stroke from a large vessel occlusion, found that thrombectomy could improve functional outcome.

Bhatia, K., et al. Association between Thrombectomy and Functional Outcomes in Pediatric Patients with Acute Ischemic Stroke from Large Vessel Occlusion. **JAMA Neurol.** 2023, Sept 1; 80(9): 910-918.

### MULTIDOMAIN PATTERNS OF CHANGE AFTER TRAUMATIC BRAIN INJURY

The TRACK-TBI LONG is a multicenter, prospective longitudinal study that was designed to assess the prevalence and patterns of cognitive, psychiatric, and functional changes following traumatic brain injury (TBI) over a seven-year period starting from a post-injury baseline.

This prospective study enrolled patients who had been hospitalized with a traumatic brain injury (TBI) between February 26, 2014, and July 27, 2018. Follow-up assessments were conducted within the first 12 months after the injury, and long-term assessments were performed up to seven years post-injury. All participants underwent evaluations using the Brief Test of Adult Cognition by Telephone (BTACT) to assess cognitive function, the Glasgow Outcome Scale-Extended (GOSE) to measure functional outcomes, and the Brief Symptom Inventory (BSI) to gauge symptoms of psychological distress. Changes in outcomes were calculated by comparing short-term and long-term assessments.

Data were analyzed for 1,264 participants including 917 with mild TBI (mTBI), 193 with moderate-severe TBI (msTBI) and a matched comparison group of 154 orthopedic trauma controls (OTCs). Aggregating the data, a decline was noted in 21% of the mild, 26% of the moderate to severe, and 15% of the orthopedic group. The highest rate of decline was for functional outcome, noted in 29% of the mTBI group and 23% of the msTBI group. Conversely, higher rates of improvement in functional outcome were observed for the msTBI group (36%) compared with the mTBI group (22%).

**Conclusion:** This prospective longitudinal study of US level 1 trauma center patients found that continued functional, cognitive, and psychiatric decline, through seven years, was notably higher in the TBI group compared with the orthopedic trauma group.

Brett, B., et al. Long-term Multidomain Patterns of Change After Traumatic Brain Injury: A TRACK-TBI

LONG Study. **Neurol**, 2023, August 15; 101(7): E740-E753.

### CULTURED STEM CELLS AND 3-DIMENSIONAL SCAFFOLD FOR CARTILAGE REPAIR

Chondral tissue of the knee has low self-repair ability, lack of vasculature and limited progenitor cell infiltration, with limited treatment options. This study reviews the one-year follow-up of a phase one trial using cultured/autologous bone marrow mesenchymal stem cells (BM-MSCs) anchored to a commercially available acellular resorbable scaffold.

This prospective open label study included six patients with symptomatic chondral lesions of the knee. Bone marrow was harvested to prepare autologous platelet rich plasma (PRP). The PRP was applied to a strip of polyglycolic and hyaluronic acid (Chondrotissue®), with this graft adhered to the lesion using Tisseel fibrin sealant. Full weight-bearing was allowed after six weeks. The primary outcome measures were the Lysholm Knee Scoring Scale (Lysholm score), Knee Injury and Osteoarthritis Outcome Score (KOOS), and pain Visual Analogue Scale (VAS).

At 12 months the Lysholm scores improved from a mean of 53 to 79.3 (p=0.03) representing clinical improvement from poor to fair. The KOOS score improved from a mean of 47.8 to 69.90 (p=0.03). The VAS pain scores improved from 34.3 to 20.8 (p=0.31). The MRI showed a good fixation and integration of the implants at 12-months post-surgery.

**Conclusion:** This study of patients with knee cartilage injuries found that treatment with a three-dimensional scaffold, combined with cultured stem cells, could improve function and pain over 12 months.

Neckar, P., et al. Treatment of Knee Cartilage by Cultured Stem Cells and Three-Dimensional Scaffold: A Phase I/IIa Clinical Trial. **Int Orthop.** 2023, Oct;47(10):2375-2382.

### FACTORS AFFECTING RESPONSE TO DIRECT CURRENT STIMULATION AMONG STROKE SURVIVORS

Transcranial direct current stimulation (tDCS) has been shown to improve post-stroke aphasia and has been used as an adjunct to traditional

therapy. This study explored the efficacy of tDCS, combined with computer-delivered speech and language therapy (SALT) for patients with subacute, stroke-induced aphasia.

The subjects were 58 right-handed adults who had experienced a stroke with aphasia within three months. The subjects completed 15, 45-minute sessions of SALT, either with or without concurrent tDCS. Those participants were randomly assigned to either a sham group or a tDCS group. Assessments included the Western Aphasia Battery-Revised (WAB-R) Aphasia Quotient (AQ), at baseline and at one, five, and twenty weeks after the final treatment session.

Age was found to be a significant factor affecting the response to tDCS as measured on the Philadelphia Naming Test (PNT). Younger individuals experienced less benefit from tDCS compared to SALT alone. In contrast, those ≥55 years of age who received tDCS showed significantly greater average improvement in naming scores on the Philadelphia Naming Test (PNT) as compared to their counterparts in the sham group. Uniquely, among tDCS recipients, higher educational attainment was linked to short-term content improvement and increased syllables per content unit.

**Conclusion:** This study of patients with subacute stroke found that age was associated with significant differences in response to direct current stimulation, with younger people experiencing less benefit than the elderly.

Stockbridge M., et al. Individual Differences in Response to Transcranial Direct Current Stimulation with Language Therapy in Subacute Stroke. **Neurorehab Neural Repair.** 2023, August; 37(8): 519-529.

### METABOLIC SYNDROME AND PROGRESSION OF KNEE OSTEOARTHRITIS

Metabolic syndrome associated osteoarthritis (MS-OA) is one of the proposed clinical phenotypes that define individuals with obesity and metabolic syndrome. This study investigated whether the metabolic syndrome and the individual components of the metabolic syndrome are associated with progression of features of knee osteoarthritis as assessed by MRI.

The subjects were 682 women participating in a knee MRI study of the Rotterdam study. The participants were assessed using questionnaires concerning their socioeconomic status, laboratory tests to determine serum HDL cholesterol, triglycerides, glucose and estradiol levels, and radiographic measurements including MRI acquisition and interpretation. The metabolic syndrome was determined and quantified using the MetS severity Z-score.

The MetS severity Z-score at baseline was associated with progression of osteophytes in all compartments of the knee, bone marrow lesions (BMLs) in the patellofemoral (PF) compartment, and cartilage defects in the medial tibiofemoral (TF) compartment. Waist circumference was associated with progression of osteophytes in all compartments as well as cartilage defects in the medial tibiofemoral compartment. High-density lipoprotein (HDL)-cholesterol levels were associated with the progression of osteophytes in the medial and lateral tibiofemoral compartment and glucose levels with osteophytes in the TF and PF compartments.

**Conclusion:** This study of women participating in the Rotterdam study found that those with higher metabolic syndrome scores at baseline experienced more severe progression of osteophytes, cartilage defects, and bone marrow lesions.

Jansen, N., et al. Metabolic Syndrome and the Progression of Knee Osteoarthritis On MRI. *Osteoarthr Cartil.* 2023, May;31(5): 647-655.

### DEPRESSION AND INCIDENCE OF DEMENTIA

Dementia is a global health concern, expected to grow as life expectancy increases. It is postulated that depression may be an early symptom of dementia, as late-life depression has been shown to be associated with a two- to five-fold increased risk for dementia. The data concerning the importance of early- and middle-life depression for the risk of dementia remains inconsistent. This study examined associations of early, middle, and late-life depression diagnoses with the incidence of dementia.

This nationwide cohort study used routinely and prospectively collected data of the Danish population-based registries from 1977-2018, and

included Danish adults of the general population, diagnosed with depression. Comparison of cohort members without depression were age and sex matched. A regression analysis was used to estimate the association between depression and dementia.

Among those with depression, 5.7% were subsequently diagnosed with dementia, compared to 3.2% in the comparison cohort. The overall hazard of dementia among those diagnosed with depression was 2.41 times that of the comparison cohort, regardless of the time elapsed from the index date and whether depression was diagnosed in early, middle, or late life. This association persisted when the time elapsed from the index date of depression was longer than 20-39 years (HR: 1.79).

**Conclusion:** This cohort study demonstrated that, regardless of what life stage depression is diagnosed, the overall risk of dementia was more than doubled in this population.

Elser, H., et al. Association of Early-, Middle-, and Late-Life Depression with Incident Dementia in a Danish Cohort. *JAMA Neurol.* 2023, Sept 1;80(9):949-958.

### FUNCTIONAL NEUROLOGICAL DISORDER IN PAIN CLINICS

Functional neurological disorder (FND) is commonly reported as a comorbidity in patients with chronic pain. This study was designed to estimate the prevalence of FND in patients seen at a chronic pain clinic and to understand how patients with chronic pain and comorbid FND differ from those without FND.

This retrospective study included consecutive patients with pain persisting for at least 12 weeks. Data collection included age, gender, pain characteristics, pain management, and pain outcome. Also included were a past or current diagnosis of FND, psychiatric disorders, and neurologic disorders.

Among the 190 patients, at least one FND was diagnosed in 32 (17%) patients. Compared to those without a diagnosis of FND, those with FND were more likely to be diagnosed with chronic, primary pain ( $p<0.0001$ ) and widespread type chronic primary pain ( $p<0.00001$ ), and less likely to suffer from secondary neuropathic pain ( $p<0.01$ ) or secondary musculoskeletal pain. In addition, those in the FND group were more likely to have a history of depression

( $p<0.05$ ), anxiety ( $p<0.05$ ), and suicide attempt ( $p<0.05$ ). The presence of comorbid FND did not significantly affect the outcome. The use of opioids and benzodiazepines was similar between the FND+ and the FND- groups.

**Conclusion:** This retrospective study found that patients with chronic pain and comorbid functional neurologic disorder have similar rates of recovery and opiate and benzodiazepine use than do those without.

Mason, I., et al. Functional Neurologic Disorder Is Common in Patients Attending Chronic Pain Clinics. *Euro J Neurol.* 2023, Sept; 30(9): 2669-2674.

### PULSED FIELD OR CONVENTIONAL THERMAL ABLATION FOR ATRIAL FIBRILLATION

For patients with drug-refractory paroxysmal atrial fibrillation (PAF), thermal ablation (TH-A) can be an effective treatment but carries a risk of damage to adjacent tissue. Pulsed field ablation (PFA) is a largely non thermal energy approach that uses microsecond scale high voltage electrical fields to cause irreversible cellular necrosis. This study compared the efficacy of these two techniques for the treatment of paroxysmal PAF.

The subjects were  $\leq 75$  years of age with symptomatic PAF, refractory to at least one antiarrhythmic drug. The patients were randomized to undergo either TH-A or PFA. After discharge, oral anticoagulation was continued according to standard guidelines and a class I or class III anti-arrhythmic drug was permitted during the initial three months post-procedure. Patients were followed for one year. For arrhythmia detection a 72-hour Holter monitor was performed at six and 12 months. The primary efficacy endpoint was freedom from a composite of; initial procedural failure, documented atrial tachycardia lasting 30 seconds or longer after three months, the use of class one or three antiarrhythmic drugs, or cardioversion after the three months.

At one year follow-up, of the 687 patients, the primary efficacy endpoint was met in 204 patients (73.3%) in the PFA group and 194 (71.3%) in the TH-A group. The primary safety endpoint occurred in

2.1% who underwent PFA and 1.5% who underwent TH-A.

**Conclusion:** This study of patients with paroxysmal atrial fibrillation receiving catheter-based therapy found that pulsed field ablation was not inferior to conventional thermal ablation for freedom from a composite of procedural failure, documented atrial tachyarrhythmia arrhythmic drug use, cardioversion or repeat ablation.

Reddy, V., et al. Pulsed Field or Conventional Thermal Ablation for Paroxysmal Atrial Fibrillation. *N Eng J Med.* 2023, November 2;389 (18):1660-1671.

### BONE MORPHOGENETIC PROTEIN SIGNALING AND OSTEOARTHRITIS

Despite the rapidly increasing global prevalence of osteoarthritis (OA), disease modifying treatments remain elusive. Recently, researchers discovered the Distal Proliferative Zone (DPZ), an area of bipotential proliferating cells which is under the influence of bone morphogenetic protein (BMP) signaling. This animal study assessed whether BMP signaling-induced transient cartilage differentiation, within the adult articular cartilage domain, is the molecular basis of the pathogenesis of OA.

Adult mice underwent anterior cruciate ligament transection (ACL) surgery to induce OA. In addition, to activate BMP signaling, tamoxifen was injected into the intraperitoneal cavity. The animals received an intra-articular injection of LDN-193189, to achieve a blockage of BMP. The animals were followed using micro-CT, histological staining, and immunohistochemistry to assess for signs of OA progression.

Micro-computed tomography ( $\mu$ CT) structural examination revealed that the ACL + vehicle group had extensive damage to articular surfaces, as well as osteophyte formation. In the studies that blocked BMP using LDN-193189 injections, the phenotypic and molecular changes of OA development were significantly curtailed following ACLT. When the intra-articular LDN-193189 injections were delayed until post-surgery day 35, the phenotypic and molecular changes of OA were reduced, but not to the extent of those treated pre-onset of OA.

**Conclusion:** This animal study suggests that bone morphogenetic

protein signaling is a critical component in the pathogenesis of osteoarthritis.

Jaswal, A., et al. BMP Signaling: A Significant Player and Therapeutic Target for Osteoarthritis. *Osteoarthr Cartil.* 2023, November; 31(11): 1454-1468.

### EARLY CRANIOPLASTY FOLLOWING POST-TRAUMATIC CRANIECTOMY

Decompressive craniectomy (DC) is a neurosurgical procedure that is used to reduce elevated intracranial pressure. The significance of the timing of the repair procedure, cranioplasty (CP) is not well understood. This study compared the outcomes of those undergoing CP at three to six months with those undergoing CP at 6-12 months after DC.

The records of patients treated between January 2010 and May 2017 were reviewed. All of the patients had undergone a DC due to raised intracranial pressure caused by a traumatic brain injury (TBI). The clinical characteristics of patients and postoperative complications that occurred within a one-year follow-up were analyzed. Neurological function was assessed with the Barthel Index (BI).

Data were analyzed from the records of 100 patients with a mean age of 37 years and a median Glasgow Coma Scale score of eight. Of these, 58 patients underwent early CP and 42 underwent late CP. Surgery-related complications occurred in 17.2% of the early group and 14.3% of the late group ( $p=0.69$ ). At one year after surgery, the BI scores improved in the early group ( $p<0.001$ ) but not in the late group ( $p=0.22$ ). In the multivariate analysis, the timing of surgery was an independent predictor of neurologic functional outcome favoring the early group ( $p=0.02$ ).

**Conclusion:** This respective study of 100 patients with traumatic brain injury who had undergone decompressive craniectomy found that those who underwent cranioplasty within three to six months had better outcomes than those with later surgical repair.

Zhao, Y., et al. Earlier Cranioplasty Following Post Traumatic Craniectomy Is Associated with Better Neurological Outcomes at One Year Follow Up: A Two Center

Retrospective Cohort Study. *Br J Neurosurg.* 2023, 37(5):1057-1060.

### BLOOD FLOW RESTRICTION TRAINING AFTER COLLES FRACTURE

Distal radial (Colles) fractures are common among those over 50 years of age. While low-load resistance training is the traditional method of rehabilitation after cast removal, this exercise recruits fewer type two fibers than does high-load resistance training. This study assessed the efficacy of blood flow resistance (BFR) training among elderly patients with Colles fractures after cast removal.

The twenty-eight subjects were 50 to 75 years of age with Colles fractures treated with casting, randomized to a BFR or non-BFR treatment group. All completed traditional rehabilitation with training sessions twice per week for six weeks. Those in the BFR group began strength training at 35% of the one repetition maximum (1 rep max). Outcome measures included the Patient-Rated Wrist Evaluation (PRWE) score, grip strength (hand dynamometer), pinch strength (mechanical pinch gauge), wrist range of motion (ROM), and muscle stiffness (digital palpation device) of the brachioradialis and abductor pollicis brevis. Measurements were taken after cast removal and at six weeks after removal.

At follow-up, compared to the controls, the PRWE scores were superior in the BFR training group ( $p=0.002$ ). The BFR group also enjoyed greater gains in grip strength ( $p=0.029$ ) and wrist range of motion ( $p=0.01$ ) as compared to the controls.

**Conclusion:** This study of elderly patients with Colles fractures found that blood flow resistance training produced better gains in strength and patient rated outcomes than did traditional rehabilitation.

Yang, M., et al. BFR Training Improves Patients Reported Outcomes, Strength, and Range of Motion after Casting for Colles Fracture. *Med Sci Sports Exer.* 2023, November; 55(11): 1985-1994.

### DYNAMIC MOTION INSTABILITY, MOTOR FUNCTION AND BALANCE AFTER STROKE

Many stroke patients suffer sensory motor cognitive and visual

deficits, with 70% of stroke patients falling within the first six months after discharge. This study assessed the efficacy of the dynamic motion instability system training (DMIST) compared to conventional rehabilitation for the treatment of motor function and balance.

Forty patients, 40-75 years of age, diagnosed with ischemic or hemorrhagic stroke were randomized to either a control group or a DMIST group. All received treatment five times per week for eight weeks. Conventional treatment included strength and proprioceptive training, passive, active-assisted, and active-resisted mobilization of the lower-limb joints; bilaterally sustained stretching of the lower-limb muscles, trunk endurance training, and stepping.

The DMIST equipment included a standing sliding plate, with a computer programmed to set the movement trajectory, speed, and repetition times for the sliding plate. The outcome measures included the Fugl-Meyer Assessment for the lower extremity (FMA-LE), and the Berg balance scale (BBS).

Both groups demonstrated significant improvement from baseline in the FMA-LE and BBS scores ( $p < 0.05$  for both), with changes in FMA-LE scores better in the DMIST group ( $p < 0.05$ ). In addition, the DMIST group demonstrated greater changes in stride length and gait speed than the control group ( $p < 0.05$ ).

**Conclusion:** This study of patients after a stroke found that dynamic motion instability training can accelerate the recovery of extremity motor function, stride length and gate speed.

Shen, J., et al. The Effects of Dynamic Motion Instability System Training on Motor Function. *Neurorehabilit.* 2023;53(1):121-130.

### HEAD INJURY AND SUBSEQUENT RISK OF FALLS

Falls are the leading cause of head injuries among older adults. The risk of a subsequent fall occurring after head injury is less well characterized. This study investigated the associations between a history of head injury and the risk of falls over 30 years.

Data were obtained from the community-based Atherosclerosis Risk in Communities (ARIC) study. This longitudinal study included community-dwelling adults 45-64

years of age at the time of enrollment in 1987-1989. The subjects were followed with annual visits through 2011 and semiannual visits since 2012. Eligible subjects had a history of head injury with or without a loss of consciousness. Falls requiring hospitalized care were recorded. Covariates included age, sex, race, education, alcohol consumption, hypertension, diabetes, and use of psychotropic medications.

Data were obtained from 13,081 participants with a mean age of 54.3 years at baseline. Over a median of 23.3 years follow-up, 28.9% had a fall requiring hospital care. For those with a head injury and a subsequent fall, the median time between head injury and fall was six years. Head injury was associated with an increased risk (Hazard Ratio, HR 2.07) of falls compared to those with no head injury. The relative association between head injury and falls was stronger among males (HR 2.60) compared with females (HR 1.80). Those with the greater number of head injuries were at a greater risk of subsequent falls, with the hazard ratio after one head injury of 1.68 and after two plus injuries, 2.37.

**Conclusion:** This cohort of community-dwelling individuals followed from 1987 through 2019 found that head injury was associated with an increased risk of falls requiring hospital care.

Hunzinger, K., et al. Associations Between Head Injury and Subsequent Risk of Falls: Results from The Atherosclerosis Risk in Communities (ARIC) Study. *Neurol.* 2023. published ahead of print.

### BREXPIPIRAZOLE FOR AGITATION IN ALZHEIMER'S

Agitation in those with dementia is common, and can have a negative effect on patient functioning, health outcomes, and quality of life. Brexpiprazole is an atypical antipsychotic that acts on noradrenergic, serotonergic, and dopaminergic neurotransmitter systems that have been implicated in the neurochemistry of agitation in Alzheimer's disease (AD). This phase three, multicenter trial assessed the efficacy of brexpiprazole for the treatment of agitation in patients with AD.

The patients were 50 to 90 years old, diagnosed with probable AD, and an onset of agitation at least two weeks prior to screening. After

screening, patients entered a 12-week double-blind study in which they were randomized at a two to one ratio to receive oral brexpiprazole at 2mg/day, 3mg/day, or a placebo. Efficacy was assessed using the Cohen-Mansfield Agitation Inventory (CMAI), a validated measure of the frequency of occurrence of 29 agitated behaviors in care facilities and community-based settings.

A total of 345 patients were randomized to receive brexpiprazole ( $n = 228$ ) or placebo ( $n = 117$ ). Both doses of brexpiprazole resulted in a greater change in CMAI from baseline to week 12. The CMAI changes indicated an overall reduction in the frequency of agitated behaviors, while CMAI factor score changes indicated improvement of three distinct types of agitated behavior: aggressive, physically nonaggressive (excessive motor activity), and verbally agitated.

**Conclusion:** This study of patients with Alzheimer's disease related agitation found that treatment with brexpiprazole could reduce episodes of agitation. Based on these data, brexpiprazole was approved in the United States for the treatment of agitation associated with dementia due to Alzheimer's disease.

Lee, D., et al. Brexpiprazole for the Treatment of Agitation in Alzheimer Dementia. a Randomized Clinical Trial. *JAMA Neurol.* doi:10.1001/jamaneurol.2023.3967.

### STATINS FOR EMBOLIC STROKE OF UNDETERMINED SOURCE

A subtype of ischemic stroke, known as Embolic Stroke of Undetermined Source (ESUS), constitutes up to one-fifth of all cases. The effectiveness of statin therapy in these instances is still unclear. This study was designed to understand the role of statins in the outcomes of patients with ESUS.

This longitudinal cohort study included consecutive adult patients with ESUS undergoing regular follow-up in an outpatient clinic. Data were collected including clinical and demographic information, comorbidities, and medical history. The history of statin use was categorized into four groups: those not using statins, those using simvastatin 20 mg, those using simvastatin 40 mg, and those using atorvastatin 40 mg. Statin use was compared with favorable functional outcome, stroke recurrence, and the

(Continued from page 2)

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composite outcome of stroke recurrence, major cardiovascular events, and death.

Over eight years, 514 patients were enrolled in the study, of which 29.8% were diagnosed as ESUS. Compared to those not using statins, those using statins had a significantly decreased risk of recurrent stroke ( $p=0.017$ ) or the composite outcome ( $p=0.023$ ). The analysis between the statin subgroups and the proportion of patients with a favorable functional outcome showed a statistically significant difference at the four-year follow-up ( $p = 0.003$ ), but not before.

**Conclusion:** This longitudinal cohort study of consecutive patients with a stroke of unknown etiology found that treatment with a statin after the stroke reduces the risk of recurrent stroke and major cardiovascular events.

Vitturi, B., et al. Effectiveness of Statins on Outcomes of Patients with Embolic Stroke of Undetermined Source (ESUS). **J Stroke Cerebrovasc Dis.** 2023, November 7; 33(1): 107469.

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