

# REHAB IN REVIEW

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## ZILEBESIRAN FOR HYPERTENSION

Hypertension is a major risk factor for ischemic heart disease, stroke, and chronic kidney disease, and is the leading preventable factor in death from cardiovascular diseases worldwide. Zilebesiran is an investigational RNA interference therapeutic agent which binds to the hepatic asialoglycoprotein receptor, reducing the production of angiotensinogen. This study evaluated the effect of this treatment on 24-hour ambulatory blood pressure in patients with hypertension.

Subjects were 18 to 65 years of age with a mean systolic blood pressure of 130 -165 mm/Hg. In part A of the study, the subjects were randomized to receive a single subcutaneous dose of zilebesiran (10, 25, 50, 100, 200, 400, or 800 mg) or placebo. In part B, a single dose of 800 mg zilebesiran or placebo was administered after initiating a low salt diet. In part C, all patients received a single 800-mg dose of zilebesiran. Patients with a systolic blood pressure of 120 mm Hg or more at week six, as assessed by 24-hour ambulatory blood-pressure monitoring, received additional treatment with irbesartan at a dose of 300 mg once daily for two weeks. The primary endpoint was the frequency of adverse events.

Compared with baseline, by week eight, a single dose of zilebesiran of at least 200 mg was associated with decreases in systolic blood pressure of more than 10 mm/Hg and in diastolic blood pressure of more than 5mm/Hg. These changes were consistent throughout the 24-hour diurnal cycle and were sustained at 24 weeks.

**Conclusion:** This study of the investigational RNA interference therapeutic drug, zilebesiran, found that a single subcutaneous dose could reduce serum angiotensin levels and blood pressure for up to 24 weeks. The most common adverse events were mild, transient injection site reactions.

Desai, A., et al. Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension. *N Eng J Med.* 2023, July 20; 389(3): 228-238.

## IMPLANTABLE SHOCK ABSORBER FOR PATIENTS WITH MEDIAL KNEE ARTHRITIS

Knee osteoarthritis has a global prevalence of 16%. Non-surgical treatment includes weight loss, analgesics, physical therapy, bracing, and intraarticular injections. As arthroscopic debridement is not considered a durable solution for this population, this study assessed the efficacy of an implantable shock absorber (ISA) for symptom relief.

This prospective study involved 10 centers in the United States and Europe, with eligible subjects between 25 and 65 years of age. All had failed at least six months of non-surgical treatments. Eighty-one subjects elected to receive an ISA. This device is 0.8 cm x 5 cm and is fixed by 2.5 cm x 4.0 cm titanium plates to the distal femur and proximal tibia. It is placed subcutaneously, outside of the joint capsule, and superficial to the medial collateral ligament (MCL). The historical control arm included subjects with knee OA who were treated with opening-wedge high tibial osteotomy (HTO). The patients were assessed with a Knee injury and Osteoarthritis Outcome Score (KOOS) and a Western Ontario and McMaster Universities Arthritis Index [WOMAC] score. The primary endpoint was a composite variable combining pain, function, specific adverse events, integrity of the hardware, and conversion to subsequent surgery.

At two years post-surgery, the composite endpoint was met by 85.6% of the ISA arm and 65.5% of subjects in the HTO arm. All five secondary endpoints demonstrated statistical superiority of the ISA arm including time to full weight bearing, and change in WOMAC pain and function scores up to 24 months.

**Conclusion:** This study of patients with osteoarthritis of the knee found that treatment with an implantable shock absorber that unloads the knee can be an effective treatment option.

Diduch, D., et al. Implantable Shock Absorber Provides Superior Pain Relief and Functional Improvement Compared with High Tibial Osteotomy in Patients with Mild-to-Moderate Medial Knee Osteoarthritis: A 2-Year Report. *Cartilage.* 2023, June: 14 (2):152-163.

## CARDIOVASCULAR SAFETY OF TESTOSTERONE REPLACEMENT

The Testosterone Replacement Therapy for Assessment of Long-Term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) trial was designed to determine the effects of testosterone replacement therapy on the incidence of major adverse cardiac events among middle-aged and older men.

This randomized phase four, double-blind placebo-controlled, noninferiority trial, recruited men without pre-existing cardiovascular disease or elevated cardiovascular risk, who were 40 to 80 years of age. Eligible subjects complained of symptoms of hypogonadism and demonstrated serum testosterone levels <300 ng/dL. The subjects were randomized to receive daily transdermal 1.62% testosterone gel or matching placebo gel, with the dose adjusted to maintain testosterone levels between 350 ng/dL and 750 ng/dL. The primary safety endpoint was the first occurrence of any component of major adverse cardiac events, death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke.

Data were completed for 5,204 patients. A first major adverse cardiac event occurred in 7% in the testosterone group and 7.3% in the placebo group. In the principal sensitivity analysis, a primary safety endpoint event occurred in 5.9% in

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the testosterone group and 5.8% in the placebo group ( $p < 0.001$  for noninferiority). A venous thromboembolic event occurred in 0.9% of the testosterone group and 0.5% of the placebo group.

**Conclusion:** This study of men with hypogonadism and preexisting or at a high risk of cardiovascular disease found that testosterone replacement therapy was non-inferior to placebo in the risk of major adverse cardiac events.

Lincoff, M., et al. Cardiovascular Safety of Testosterone Replacement Therapy. *N Eng J Med.* 2023, July 13;389(5): 107-117.

## **MYOCARDIAL INFARCTION AND COGNITION**

An understanding of the vascular contributions to cognitive decline may help identify potential targets to slow or prevent dementia. As myocardial infarction (MI) is a severe manifestation of coronary artery disease (CAD), this study was designed to assess whether incident MI is associated with faster long-term cognitive decline.

Data were obtained from six prospective cohort studies, conducted from 1971 to 2019. The subjects were individuals who were identified with no history of dementia or stroke at baseline. All subjects had one or more cognitive assessments, while individuals with an incident MI had one or more cognitive assessments before and one or more assessments after the MI. The primary outcome measure was change in global cognition. Secondary outcomes were changes in memory and changes in executive function. Covariates included age, sex, educational level, race and ethnicity, waist circumference, body mass index, fasting glucose level, low density lipoprotein cholesterol levels, systolic blood pressure, use of anti-hypertensive medications, current tobacco abuse, physical activity, and alcohol drinks per week.

The total study cohort included 30,465 individuals with a mean age of 64 years and a median follow-up of 6.4 years. Of these 1,033 had one or more MI events. An incident MI was not associated with an acute decrease in global cognition, executive function or memory. However, compared to those without an MI, the rate of decline in global cognition, memory, and executive function was significantly faster over the years for adults after an MI.

**Conclusion:** This study found that incident myocardial infarction was associated with accelerated cognitive decline during the years after their myocardial infarction.

Johansen, M., et al. Association Between Acute Myocardial Infarction and Cognition. *JAMA Neurol.* 2023; 80(7) :665–667.

## **CAUSES OF READMISSION AMONG INDIVIDUALS WITH TRAUMATIC SPINAL CORD INJURY**

People with spinal cord injuries (SCIs) often experience serious secondary medical and non-medical problems. In recent years, the increase in the age of incidence and in life expectancy has resulted in chronic secondary conditions. Several of these can cause readmission to health facilities.

This prospective observational cohort study was conducted by the Italian Spinal Cord Injury (SCI) study Group, involving 31 specialized SCI centers from 13 Italian regions. Readmissions after hospitalization for a traumatic SCI were recorded. Data collection included demographic characteristics and medical data including level and severity of injury. For the statistical analysis, the level and severity grade of injury were grouped as AIS ABC-paraplegia (T1-S5 ABC); AIS ABC-tetraplegia (C1-C4 ABC, C5-C8 ABC); and all D.

Of the consecutive readmissions, 1,039 adults with a mean age of 46 years met the inclusion criteria. The most frequent complications were urologic diagnoses ( $n=614$ ), pressure injuries ( $n=413$ ), and spasticity ( $n=368$ ). In 311 readmissions (30%), only one cause was recorded, in 703 (68%) two or more causes were registered (in 25, 2%, missing). In the multivariate analysis conditions associated with a longer length of stay included coming from other places rather than home, coming from another region, not being classified in the group all D, and recording more than one diagnosis as the cause of readmission.

**Conclusion:** This study of patients with spinal cord injury found that the most common causes of readmission were urologic followed by pressure injury and spasticity.

Franceschini, M., et al. Causes and Length of Stay of Readmission Among Individuals with Traumatic Spinal Cord Injury: A Prospective Observational Cohort Study. *Spinal Cord.* 2023, July; 61(7): 383-390.

## OREXIN RECEPTOR AGONIST FOR NARCOLEPSY

Narcolepsy is a rare disorder of hypersomnolence, characterized by excessive daytime sleepiness. Low to absent orexin levels in the cerebrospinal fluid support a diagnosis of narcolepsy type 1. Orexins act through two G-protein-coupled receptors, orexin receptor 1 (OX1R) and orexin receptor 2 (OX2R), both of which are widely distributed in the brain. This study assessed the treatment efficacy of a highly selective oral OX2R agonist, TAK-994, which crosses the blood-brain barrier.

The TAK-994-1501 trial recruited patients with narcolepsy type 1, who were randomized to receive TAK-994 30 mg, 90 mg, 180 mg, or placebo. The primary endpoint was the change from baseline to week eight in average sleep latency on the Maintenance of Wakefulness Test (MWT). The secondary endpoints included the change in the weekly cataplexy rate and the change in the Epworth Sleepiness Scale (ESS).

Of the 73 subjects, primary endpoint data were available for 41 patients with most missing data due to early trial termination. The changes from baseline to week eight in average sleep latency on the MWT were 23.9 minutes in the 30 mg group, 27.4 minutes in the 90 mg group, 32.6 minutes in the 180 mg group, and -2.5 minutes in the placebo group ( $p < 0.001$  for all compared to placebo). In addition, scores on the ESS improved more in the treatment groups than in the placebo group ( $p < 0.001$ ) for all comparisons. Finally, improvement in cataplexy rates decreased more in all treatment groups than in the placebo group ( $p = 0.001-0.02$ ).

**Conclusion:** This randomized, controlled trial of patients with type 1 narcolepsy found that treatment with an orexin receptor 2 agonist could significantly improve sleep scores.

Dauvilliers, Y., et al. Oral Orexin Receptor 2 Agonist in Narcolepsy Type 1. *N Eng J Med.* 2023, July 27; 389(4): 309-321.

## ADJACENT SEGMENT DISEASE AFTER LUMBAR ARTHROPLASTY VERSUS FUSION

For patients with degenerative disc disease (DDD) who fail to respond to conservative measures, surgical intervention may be considered. Among the most common surgical interventions are

anterior lumbar interbody fusion (ALIF) and lumbar disc arthroplasty (LDA). This study compared the rates of post-operative adjacent segment disease (ASD) between those receiving ALIF and those receiving LDA.

The subjects were adults who underwent one to two-level surgical intervention between January 2010 and October 2022, receiving either an ALIF or an LDA. The groups were matched according to factors associated with the risk of ASD. The primary outcome was the development of ASD, defined as any subsequent arthrodesis, laminectomy/decompression, or spinal instrumentation surgery at the adjacent level within 36 months of the index surgery.

The matched cohort contained 3,074 individuals with DDD who underwent elective spine surgery, including LDA (1,625) and ALIF (1,625). At three years the rate of adjacent segment syndrome (ASD) was 14.5% in the ALIF group and 6.6% in the LDA group ( $p < 0.001$ ). The mean duration of development of ASD was 3.9 years in the ALIF group and 9.2 years in the LDA group.

**Conclusion:** This study of patients with degenerative disc disease who underwent elective spine surgery found that the risk of adjacent segment deterioration was greater among those who were treated with anterior lumbar interbody fusion than those treated with a lumbar disc arthroplasty.

Shukla, G., et al. Lumbar Arthroplasty Is Associated with a Lower Incidence of Adjacent Segment Disease Compared With ALIF: A Propensity-matched Analysis. *Spine.* 2023, July 15;48(14):978-983.

## BRAIN-DERIVED NEUROTROPHIC FACTOR AND POST-STROKE PROGNOSIS

Neurotrophins play a critical role in the development, function, and survival of neurons. Brain-derived neurotrophic factor (BDNF) is known to regulate neuroregeneration, neuroprotection, and synaptic plasticity by activating tropomyosin-related kinase receptor B. This study assessed the association of serum BDNF levels with outcomes after ischemic stroke.

Data were from the China Antihypertensive Trial in Acute Ischemic Stroke, involving adult patients with a first-ever stroke from 26 hospitals across China. Fasting blood samples were collected within

24 hours of hospital admission with serum BDNF measured. The participants were followed at three months after the stroke with evaluations including the Modified Rankin Scale (mRS) score. The primary outcome was the combination of death and major disability (mRS 3-6).

Data were available for 3,319 patients with a mean age of 61.8 years, and a median BDNF concentration of 32.87 ng/ml. During three months of follow-up 24.92% of the patients experienced a primary outcome, including 734 with major disability and 93 deaths. In an adjusted analysis, compared to those in the lowest tertile of BDNF, those in the highest tertile had a decreased risk of the primary outcome ( $p = 0.009$ ), major disability ( $p = 0.038$ ), death ( $p = 0.035$ ), and the composite of death and vascular events ( $p = 0.021$ ).

**Conclusion:** This large-scale multicenter prospective study of patients with an acute ischemic stroke found that those with the highest levels of brain-derived neurotrophic factor had a 27% percent decrease in the risk of death and major disability.

Zhu, Y., et al. High Serum Brain-Derived Neurotrophic Factor is Associated with Decreased Risks of Poor Prognosis After Ischemic Stroke. *Stroke.* 2023, July; 54(7): 1789-1797.

## ACUPUNCTURE ADDED TO REHABILITATION FOR POST-STROKE CARE

Stroke is the second leading cause of mortality and a major source of disability globally. Post-stroke cognitive impairment is a pervasive syndrome, recognized in more than 70% of patients with stroke. As some studies have demonstrated the efficacy of acupuncture for the treatment of patients with stroke, this study assessed the effect of adding acupuncture to other rehabilitation treatments on cognition and functional recovery.

This literature review and meta-analysis included 42 papers that included acupuncture with more traditional stroke therapy. The data were pulled from the studies and a meta-analysis was performed. Of these, 18 were randomized controlled trials with a total of 1,654 patients. The outcome measures included the Mini-Mental Status Exam (MMSE), the Montreal Cognitive Assessment (MoCA), the Modified Barthel Index

(MBI), and the Fugl-Meyer Assessment (FMA).

Of the 12 studies that included an MMSE, the acupuncture group had significantly better outcomes at follow-up than did the control ( $p < 0.00001$ ). Of the studies that included a MoCA, the meta-analysis demonstrated superior outcomes in those treated with acupuncture, compared to the controls ( $p < 0.00001$ ). In addition, better outcomes were noted with the addition of acupuncture in studies that used the MBTI and FMLA ( $p < 0.001$  for both).

**Conclusion:** This meta-analysis of patients in an inpatient rehabilitation facility for a stroke found that adding acupuncture to routine treatment can improve functional and cognitive outcomes.

Zhuo, P., et al. Efficacy and Safety of Acupuncture Combined with Rehabilitation Training for Post Stroke Cognitive Impairment: A Systematic Review and Meta-Analysis. *J Stroke Cerebrovasc Dis.* 2023, September; 32(9):107231.

### TRIGEMINAL NERVE STIMULATION FOR PROLONGED DISORDERS OF CONSCIOUSNESS

As previous studies have demonstrated that trigeminal nerve stimulation (TNS) may reduce levels of inflammatory biomarkers, blood brain barrier permeability dysfunction, and brain edema, this study assessed the effect of TNS in patients with prolonged disorders of consciousness.

The sample comprised 60 adult patients, hospitalized between January of 2021 and September of 2022 at Sun Yat-sen Memorial Hospital. All subjects had experienced a loss of consciousness of longer than 28 days and had been diagnosed as being in a vegetative or minimally conscious state (MCS). The patients were randomized to receive a sham treatment or active TNS, applied at the first and second branches of the trigeminal nerve using 10-15 milliamps at 40 Hertz and a pulse width of 200 microseconds. The treatment sessions were performed for three hours per day, five days per week for four weeks. Outcome measures included the Coma Recovery Scale-Revised (CRS-R) and the Glasgow Coma Scale (GCS), with FDG-PET scanning used as an objective assessment of brain function.

At follow-up, compared to the sham group, greater improvements were noted for the treatment group in

mean scores of the CRS-R (two-week:  $p=0.006$ ; four-week:  $p<0.001$ ; eight-week:  $p<0.001$ ; 12-week:  $p<0.001$ ) and the GCS (four-week:  $p=0.002$ ; eight-week:  $p<0.001$ ; 12-week:  $p=0.003$ ). At 12 weeks the number of patients emerging from MCS in the TNS group was significantly higher than in the sham group. The FDG-PET scans found that, compared with baseline, the active TNS group demonstrated greater metabolism in the right parahippocampal cortex, right precuneus, and bilateral middle cingulate cortex within two weeks of treatment. No such changes were noted in the sham group.

**Conclusion:** This study of patients with disorders of consciousness found that percutaneous stimulation of the trigeminal nerve may be effective for improving level of consciousness.

Ma, H., et al. Trigeminal Nerve Stimulation for Prolonged Disorders of Consciousness: A Randomized, Double-Blind, Sham Controlled Study. *Brain Stim.* 2023, May-June;16(3):819-827.

### DECOMPRESSION OF CALCIFIC TENDONITIS OF THE SHOULDER

Calcific tendonitis of the shoulder is a common condition, with conventional wisdom suggesting that these are most often reabsorbed. However, several studies have described means by which these deposits can be removed including ultrasound guided percutaneous drainage or lavage as well as extracorporeal shockwave therapy. This study assessed the efficacy of arthroscopic removal of the deposits.

The study patients were seen between December 2013 and August 2019, and identified as having undergone arthroscopic surgery for the removal of calcific deposits from the shoulder. Before surgery, radiographs, CT and MRI scans were assessed for the location and size of the deposits. All underwent a clinical assessment including a preoperative visual analog scale (VAS) pain score, as well as evaluations of range of motion (ROM) and function with the American Shoulder and Elbow Surgeons (ASES) scores.

Of the 99 patients assessed, calcific deposits were most commonly found in the supraspinatus (64%) followed by the infraspinatus (20.2%), and the subscapularis (15.2%). Compared to preoperative scores, the postoperative scores on the VAS and ASES were improved at follow-up.

Overall, 33 of 99 patients (33.3%) had improved VAS and ASES scores within two weeks.

**Conclusion:** This retrospective study of patients with calcific tendonitis of the shoulder found that arthroscopic debridement of the calcific deposits was associated with improvement in pain and function, with most of that improvement occurring within four weeks.

Yoon, E., et al. Arthroscopic Decompression of Calcific Tendonitis Without Cuff Repair. *Bone Joint J* 2023;105-B (6):663-667.

### SKIPPING BREAKFAST AND COGNITIVE DECLINE IN OLDER ADULTS

A recent systematic review, including 24 studies performed in children and adolescents, suggested that skipping breakfast induces adverse effects on cognitive function tasks requiring attention, executive function, and memory on the same morning. This study was designed to determine whether skipping breakfast is associated with long-term changes in cognitive function among older adults.

Data were obtained from the HEIJO-KYO cohort, conducted between September and April from 2010 to 2014, including 1,127 community-dwelling people  $\geq 60$  years of age. The subjects were asked how many days a week they skipped breakfast, using a standardized questionnaire at baseline. Cognitive function was assessed using the Mini Mental State Exam (MMSE). Energy intake was assessed using the Food Frequency Questionnaire.

Data analysis was completed for 712 subjects with a mean age of 70.8 years. During follow-up (median, 31 months), 135 of 712 participants demonstrated a decline in their cognitive scores. The mean MMSE score demonstrated a greater decline among those who skipped breakfast ( $p < 0.006$ ). Dietary analysis found that breakfast skippers consumed a significantly lower amount of vegetables, fruits and fish than did those who ate breakfast. This resulted in lower daily intakes of dietary fiber, potassium, and major vitamins such as B1, C, A, D, E, and K.

**Conclusion:** This study of community dwelling elderly found that skipping breakfast is independently associated with a subsequent decline in cognitive scores.

Ishizuka, R., et al. Breakfast Skipping and Declines in Cognitive Scores among Community-Dwelling Older Adults: A Longitudinal Study of the HEIJO-KYO Cohort. *J Geriatr Psych Neurol.* 2023 Jul;36(4):316-322.

### GREATER OCCIPITAL NERVE BLOCK FOR CLUSTER HEADACHE

Cluster headaches (CHs) have often been described as the most painful condition that a patient has ever experienced. Greater occipital nerve blocks (ONBs) have been found to be efficacious for the short-term preventative treatment for patients with occipital neuralgia. This systematic review assessed the efficacy of these blocks for patients with CHs.

A literature review was completed for studies of patients with the diagnosis of CH who were treated with ONB with a combination of local anesthetic and/or corticosteroid. Measurements were made in change in the frequency, severity, and duration of attacks as well as a proportion of those who responded to the treatment.

From the literature review, one randomized controlled trial demonstrated a greater reduction in the mean number of attacks per day in the treatment group compared to the control group. In the five studies that used a pain visual analog scale (VAS) score, significant improvement was noted in the mean pain scores after the blockade, which persisted at six months after treatment. Four reported significant reductions in the mean duration of attacks after the injections. Both randomized controlled trials demonstrated a reduction in attack frequency over short time frames. The proportion of participants who responded in studies ranged from 46.7% to 100%.

**Conclusion:** This literature review found that occipital nerve blocks could be an effective treatment for cluster headaches.

Gordon, A., et al. Effectiveness and Safety Profile of Greater Occipital Nerve Blockade in Cluster Headache: A Systematic Review. *J Neurosurg Neurosurg Psych.* 2023. doi:10.1136/jnnp-2023-331066.

### INTRAVENOUS AND INTRA-ARTICULAR STEROID AFTER TOTAL KNEE ARTHROPLASTY

Up to a quarter of patients who undergo total knee arthroplasty (TKA)

experience post-operative pain. This study was designed to determine the efficacy of intravenous (IVS) and periarticular (PAS) corticosteroid injections for the treatment of patients after TKA.

This parallel, randomized, clinical trial (RCT) involved 178 patients who underwent primary, unilateral TKA. Those subjects were randomized to receive a placebo (P), IVS, PAS, or IVS+PAS (IVPAS). Post-operatively the patients were evaluated daily for three days for pain scores at rest, pain during movement, flexion range, quadriceps strength, and distance walked.

For pain during movement, the IVS and IVSPAS groups had better scores than did the P group, as measured at 24, 48, and 72 hours ( $p \leq 0.023$  for all). In addition, compared to the P group, the IVSPAS subjects had better flexion range of motion ( $p=0.027$ ) and quadriceps power at post-operative days two and three ( $p=0.005$ ) and ( $p=0.007$ ), respectively, and were able to walk greater distances in the first three days ( $p<0.003$ ).

**Conclusion:** This study of patients undergoing total knee arthroplasty found that combining intravenous and periarticular corticosteroids resulted in improved post-operative pain and mobility.

Chan, P., et al. Pain Relief after Total Knee Arthroplasty with Intravenous and Periarticular Corticosteroid: A Randomized, Controlled Trial. *J Bone Joint Surg-Am.* 2023, June 21; 105(12): 924-932.

### PAIN TRAJECTORIES AMONG U.S. VETERANS DURING COVID-19

In a study of Canadian military veterans, early in the COVID-19 pandemic, participants reported increased pain, thought to be associated with reductions in treatment access and increased psychosocial distress. This study reviewed reports of pain among U.S. veterans prior to and during the COVID-19 pandemic.

Subjects were military veterans, 18 to 40 years of age, recruited in February of 2020 for a survey of health behaviors and attitudes among young adult veterans recruited outside of health care settings. The participants were invited to complete additional follow-up surveys up to 12 months after the World Health Organization declared COVID-19 a global pandemic in March of 2020. Measurements were made of pain, sociodemographic characteristics,

childhood trauma, combat exposure, physical pain intensity, negative reactions to COVID-19, and loneliness.

Data were obtained from participants with an average age of 34.5 years at baseline, with 95.8% reporting at least some pain at baseline and 50.2% reporting severe pain. The trajectories of pain were characterized into four pain trajectory classes: 1) Chronic Pain (17.3%); 2) Decreasing Pain (57.2%); 3) Stable Mild Pain (19.8%); and 4) Increasing Pain (5.7%).

The pain intensity improved from a mean baseline score of 6.9/10 to a mean follow up score of 1.4/10. At nine-month follow-up, 10.12% reported loneliness, 1.76% reported childhood trauma, and 0.64 reported negative reactions to COVID-19. Those with childhood pain were more likely to have chronic pain, as were those with combat exposure. Loneliness was consistently associated with subsequent pain.

**Conclusion:** This study of American military veterans found that most of those sampled reported a decrease in their pain during the COVID-19 crisis.

Saba, S., et al. Pain Trajectories among U.S. Veterans during COVID-19. *J Pain.* 2023, July 4. In press. <https://doi.org/10.1016/j.jpain.2023.06.018>.

### SIGNIFICANCE OF VISUAL DYSFUNCTION AFTER SPORT-RELATED CONCUSSION

Children have the highest rates of concussion in sports, with the typical duration of recovery less than one month. However, approximately 30% take longer to recover, a condition typically referred to as persistent post concussion syndrome (PPCS). This study is a secondary analysis of a randomized controlled trial, to assess whether exercise induced visual dysfunction is associated with PPCS.

This multicenter, randomized, clinical trial included adolescent athletes, ages 13 to 18 years, presenting with a sports related concussion within 10 days of injury. Clinical assessments included the King-Devick (KD) measure, performed at rest before and again two minutes after completing the Buffalo Concussion Treadmill Test. The primary outcome variable was recovery from PPCS.

Data were completed for 99 adolescents who were randomly assigned to perform aerobic exercise or to a placebo stretching program.

Forty-four demonstrated exercise-induced vision dysfunction (EIVD). The mean recovery time for those with EIVD was 48.14 days, while that for those without EIVD was 21.95 days ( $p < 0.001$ ). Those who demonstrated EIVD at the initial evaluation developed PPCS at a significantly greater rate than did those without visual symptoms (71% versus 34%;  $p < 0.001$ ).

**Conclusion:** This study of adolescent athletes with a sports related concussion found that exercise induced visual dysfunction was significantly related to persistent post-concussive symptoms.

Vernau, B., et al. Exercise-Induced Vision Dysfunction Early after Sport-Related Concussion Is Associated with Persistent Post-Concussive Symptoms. *Clin J Sports Med.* 2023, July;33 (4): 388-394.

### TRENDS IN POST-OPERATIVE GABAPENTINOIDS AND OPIOIDS AMONG OLDER ADULTS

Older adults (ages  $\geq 65$  years) account for almost half of surgeries each year in the U.S. Postoperative pain management is a critical part of surgical care and is often included among quality measurement efforts. Gabapentinoids are listed in the American Geriatrics Society Beers Criteria, which include a strong recommendation to avoid using gabapentinoids with opioids except when transitioning from one to the other. This study was designed to better understand trends in prescribing of both postoperative gabapentinoids and concomitant opioids over a recent period.

Data were merged from the Medicare Carrier, Medicare Provider Analysis and Review (MedPAR), and Outpatient Files with Medicare Part D to obtain a representative sample of 20% of the total population of individuals  $\geq 65$  years of age who had undergone one of the 14 most common non-cataract surgeries. The charts of gabapentinoid-naïve patients were reviewed to determine the rate and duration of post-operative gabapentinoids. In addition, the proportion of postoperative prescribing of new gabapentinoids was reviewed for each year from 2014 to 2018.

Using data obtained from April of 2022 to April of 2023, the cohort included 494,922 patients with a mean age of 73.7 years. Of these, 18,095 (3.7%) received a new gabapentinoid prescription. An adjusted analysis revealed that the

rate of new postoperative gabapentinoid prescribing increased from 2.3% in 2014 to 5.2% in 2018 ( $p < 0.001$ ). In this same period, opioid prescribing increased from 56% to 59% ( $p < 0.001$ ). Concomitant prescribing also increased from 1.6% in 2014 to 4.1% in 2018 ( $p < 0.001$ ).

**Conclusion:** This cross-sectional study of a sample of US Medicare recipients undergoing surgery found that new postoperative gabapentinoid prescriptions have increased without a decrease in patients receiving postoperative opioids.

Bongiovanni, T., Trends in the Use of Gabapentinoids and Opioids in the Postoperative Period among Older Adults. *JAMA Network Open.* 2023, Jun; 6(6): e2318626.

### GLYMPHATIC FUNCTION AND COGNITIVE DECLINE

The glymphatic system is a recently discovered waste clearance system in the brain that plays a crucial role in removing metabolic waste and toxins from the brain tissue. As the Diffusion Tensor Imaging Along the Perivascular Space (DTI-ALPS) index has been shown to reflect glymphatic function, this study used the DTI-ALPS index to measure the effect of glymphatic function on age and cognitive function.

This retrospective study included subjects involved in the Cognitive Impairment, Retinopathy, and Cerebrovascular Lesions in the Elderly (CIRCLE) study. This prospective observational study included subjects 40 years of age or older and free of known dementia or stroke. The subjects underwent evaluation using multi-model magnetic resonance imaging (MRI) scans with DTI-ALPS index calculation and Mini-Mental State Examinations (MMSE). The data were reviewed for associations between the DTI-ALPS index and MMSE decline.

Data were evaluated for 633 older adults with an average age of 62.8 years. In the cross-sectional study, the DTI-ALPS index was positively associated with the MMSE score. In the longitudinal study, 164 participants completed the follow up neuropsychological examination. A regression analysis found that a lower DTI-ALPS index was an independent predictor of cognitive decline ( $p = 0.007$ ). The DTI-ALPS index declined progressively with ageing ( $p < 0.001$ ), and the decrease was more pronounced after 65 years of age.

**Conclusion:** This study found that glymphatic function seems to play a role in protecting the brain against age-related cognitive decline.

Wang, J., et al. Glymphatic Function Plays a Protective Role in Age-Related Cognitive Decline. *Age Ageing.* 2023, July 1; 52(7): 1-8.

### EFFECT OF COCOA EXTRACT AND A MULTIVITAMIN ON COGNITIVE FUNCTION

With the aging of the global population, it is critical to identify effective strategies to preserve cognitive function. Previous studies have suggested that there may be cognitive benefits of cocoa flavanols. In addition, there is evidence that multivitamin-mineral (MVM) alone or with other dietary supplements may enhance global cognitive function in older adults ( $\geq 65$  years). This study investigated whether daily treatment with cocoa extract (CE) and/or a MVM could be protective of cognitive function in older adults.

The COSMOS-Mind (Cocoa Supplement and Multivitamin Outcomes Study of the Mind) was an ancillary study to a large pragmatic, placebo-controlled,  $2 \times 2$  factorial clinical trial. The subjects were 2,262 individuals  $\geq 65$  years of age without a history of MI, or cancer. The subjects were randomized to receive a placebo or a MVM (Centrum Silver) daily. The primary outcome was a global composite from mean standardized (z) scores (relative to baseline) from individual tests, including the Telephone Interview of Cognitive Status, Word List and Story Recall, Oral Trail-Making, Verbal Fluency, Number Span, and Digit Ordering.

Of the original subjects 1,732 completed all three years of follow-up. Cocoa extract had no effect on global cognition. Compared to those who received a placebo, those who received a daily MVM supplementation had superior global cognition ( $p = 0.007$ ) both for memory ( $p = 0.04$ ) and for executive function ( $p = 0.02$ ). This effect was most pronounced in participants with a history of cardiovascular disease.

**Conclusion:** This large scale randomized controlled trial found that a daily dose of a multivitamin with mineral preserved global cognition memory and executive function, while cocoa had no such positive effects.

Baker, L., et al. Effects of Cocoa Extract and a Multivitamin on Cognitive Function: A Randomized

### WEEKEND REHABILITATION AND HOSPITAL MORTALITY IN HIP FRACTURE

Previous studies have demonstrated the effects of early rehabilitation on the outcomes of patients undergoing hospitalization. This study investigated the association between weekend rehabilitation and hospital mortality after hip fracture surgery.

This retrospective cohort study was conducted using a Japanese nationwide multi-center database including 572,181 patients who received hip fracture surgery over eight years. Propensity score matching was performed, comparing those who had received additional rehabilitation on the weekend in addition to routine, weekday rehabilitation. The groups were compared by mortality and medical complications.

Patients with additional weekend rehabilitation had a lower hospital mortality rate compared to the weekday-only group ( $p < 0.001$ ). In addition, systemic complications such as acute coronary syndrome, heart failure, and renal failure as well as sepsis were lower in the weekend group. Complications that were higher in the weekend group included urinary tract infection, surgical site infection, and hematoma.

**Conclusion:** This retrospective study of patients undergoing hip surgery found that additional rehabilitation on the weekend was associated with lower in-hospital mortality as well as lower cardiac, renal, and infectious disease complications.

Ogawa, T., et al. Association Between Additional Weekend Rehabilitation and In-Hospital Mortality in Patients with Hip Fractures A Propensity Score Matching Analysis in a Multicentre Database. **Bone Joint J.** 2023, August 1; 105-B (8): 872-879.

### UNDIAGNOSED RISK FACTORS IN ISCHEMIC STROKE

The incidence of undiagnosed major vascular risk factors (UMRFs) among patients with new ischemic stroke (IS) is not well known. Risk factors for stroke, that are well known in the medical community include active smoking, obesity, mechanical heart valves, depression/sarcoidosis, alcohol abuse, history of stroke,

transient ischemic attack, and retinal ischemia. The study excluded these risk factors in their analysis and reviewed the frequency and effect of undiagnosed risk factors of hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation/flutter, and other structural cardiac disease.

This retrospective study included data from the ASTRAL database of acute stroke patients admitted within 24 hours of the last known well time. Major risk factors were defined according to the INTERSTROKE study.

Data analysis included 4,354 eligible subjects with a median age of 70 years. At the time of the stroke 25.8% had no previously unidentified MRFs. Among those with no previously identified risk factors, a MFR was identified at admission in 69.7%. Of those in the group with UMRFs (apparently 'healthy') UMRF group patients were diagnosed with dyslipidemia (61.4%), hypertension (23.7%) and atrial fibrillation (10.2%), respectively. In the group with previously identified major risk factors, newly diagnosed risk factors at the time of the stroke included hypertension (8.6%), dyslipidemia (37.9%), diabetes mellitus (4.1%), atrial fibrillation (11.2%), low ejection fraction (2.4%) and coronary artery disease (1.7%).

**Conclusion:** This large single center study found that 69.7% of patients presenting with a new ischemic stroke had undiagnosed major risk factors of which the most common were dyslipidemia, hypertension, and atrial fibrillation.

Rego, A., et al. Undiagnosed Major Risk Factors in Acute Ischemic Stroke Patients: Frequency, Profile, Stroke Mechanisms and Outcome. **Europ J Neurol.** 2023. Early View. DOI: 10.1111/ene.16028

### NUSINERSEN FOR SPINAL MUSCULAR ATROPHY: FIVE-YEAR UPDATE

Spinal muscular atrophy (SMA) is caused by a homozygous deletion or other pathogenic variants of the survival motor neuron 1 (SMN1) gene. A paralogous SMN2 gene provides sufficient survival motor neuron (SMN) protein to sustain partial motor neuron development prenatally but cannot prevent later neurodegeneration. Nusinersen is an antisense oligonucleotide that promotes the expression of functional SMN protein by altering pre-messenger RNA splicing. The NURTURE study is an ongoing study evaluating the safety and efficacy of

nusinersen in infants likely to develop SMA Type I or II, who initiated treatment before the onset of overt clinical signs or symptoms of SMA.

Twenty-five infants were enrolled, 15 with two SMN2 copies, and ten with three SMN2 copies. The nusinersen treatment regimen consisted of four loading doses (administered on days 1, 15, 29, and 64), followed by a maintenance dose every 119 days over five years. The primary endpoint was time to death or respiratory intervention (invasive or noninvasive for  $\geq 6$  h/day continuously for  $\geq 7$  days or tracheostomy).

At the five-year update, the median age of the children was 4.9 years. All were alive, and no change in respiratory intervention occurred since the three-year follow up. Children with three SMN2 copies achieved all World Health Organization (WHO) motor milestones, with all but one milestone in one child within normal developmental timeframes. All 15 children with two SMN2 copies achieved sitting without support, 14/15 walking with assistance, and 13/15 walking alone.

**Conclusion:** This study of children with two or three SMN2 copies found that nusinersen, initiated in the presymptomatic stage, resulted in previously unattainable motor milestones.

Crawford, T., et al. Continued Benefit of Nusinersen Initiated in the Presymptomatic Stage of Spinal Muscular Atrophy: 5-Year Update of the NURTURE Study. **Musc Nerve.** 2023, August;68(2):157-170.

### LONG-TERM FOLLOW-UP AFTER MINOR ISCHEMIC STROKES OR TRANSIENT ISCHEMIC ATTACKS

While the worldwide age-standardized incidence of stroke is decreasing, it is increasing among younger individuals. This study investigated the rate of recurrent strokes or other vascular events in young adults with ischemic stroke (IS) or transient ischemic attacks (TIA).

Data were obtained from The Stroke in Young Fabry Patients (SIFAP) study, a prospective investigation of stroke patients 18 to 55 years of age. The initial study included 5,023 adults from 47 centers. From these subjects, 396 were invited for a ten-year follow-up. These data were analyzed to determine the cumulative ten-year risks for future events using life-table functions, and cumulative incidence rates per 1,000 person-years.



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At a median follow-up of 11.8 years, 42 (10.6%) patients had a recurrent IS, 25 (6.3%) patients had a TIA, four (1.0%) patients had an intracerebral hemorrhage, two (0.5%) patients had a subarachnoid hemorrhage, 20 (5.1%) had an acute coronary syndrome, nine (2.3%) patients had a systemic embolism or peripheral arterial thrombosis, nine (2.3%) patients had a deep venous thrombosis, and three (0.8%) patients had a pulmonary embolism. A total of 27 (6.8%) patients died during follow-up. Of these 12 (3.0%) patients died due to a vascular cause. The prevalence of cardiovascular risk factors increased over time, and 22 (13.5%) patients lacked any secondary preventive medication at the in-person follow-up.

**Conclusion:** In this multicenter cross-sectional study of 396 patients ages 18-55, researchers found that at approximately 10-year follow-up, 1/5 of the patients had a recurrent vascular event and nearly 1/6 had a recurrent cerebrovascular event.

Broman, J., et al. Long-Term Risk of Recurrent Vascular Events and Mortality in Young Stroke Patients: Insights from a Multicenter Study. *Europ J Neurol*. 2023, September; 30(9): 2675-2683.

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