

# REHAB IN REVIEW

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## PERIPHERAL NERVE STIMULATION AND LONG-TERM MEMORY

Among current neuromodulatory interventions, transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) have both shown promise as non-invasive and well tolerated procedures. This study compared the effects of tDCS and tACS on associative memory performance.

This randomized controlled trial included 85 healthy adults. The participants were engaged in a word association task consisting of Swahili-English vocabulary learning while receiving, occipital nerve (ON)-tDCS (ON), sham tDCS (sham), 40 Hz ON-tACS (40Hz), or 1 Hz ON-tACS (1Hz). The verbal paired-association memory task was divided into three blocks with each block consisting of a study period followed by a 30 second rest period, and a test period. On day seven the subjects repeated the recall test. At baseline and follow-up salivary  $\alpha$ -amylase, was measured as a marker of endogenous noradrenaline activity. The primary outcome was the number of word associations learned and then correctly recalled.

On day one, the cumulative number of words learned was greater in the 40 Hz group than either the 1 Hz group ( $p=0.01$ ), the ON group ( $p=0.03$ ), or the sham group ( $p=0.02$ ). On day seven, more words were recalled by those in the ON, than those in the 1Hz ( $p=0.04$ ) or sham ( $p<0.001$ ). In a review of the percentage of words forgotten from day one to day seven, those in the ON group forgot fewer words than those in the 40Hz group ( $p=0.04$ ) and the sham group ( $p=0.009$ ). An increase in salivary  $\alpha$ -amylase was noted in the ON-tDCS and the 40 Hz ON-tACS groups but not in the sham or 1Hz ON-tACS group.

**Conclusion:** This study found that learning during a word association task was enhanced with tDCS delivered at 40Hz, and long-

term memory was enhanced by both tDCS and tACS.

Luckey, A., et al. Potential Role for Peripheral Nerve Stimulation on Learning and Long-Term Memory: A Comparison of Alternating and Direct Current Stimulations. *Brain Stimul.* 2022. May-June;15(3): 536-545.

## AQUATIC THERAPY FOR CHRONIC LOW BACK PAIN

Among patients with back pain, recent reviews have suggested that therapeutic aquatic exercise can reduce pain intensity and improve function. However, no study has compared the long-term efficacy of aquatic therapy or compared this treatment to traditional physical therapy for patients with chronic back pain.

Patients were adults 18-65 years of age with low back pain, with or without lower limb pain, for at least three months. Patients were randomized to 12 weeks of therapy, 60 minutes twice per week for a total of 24 treatment sessions. Those randomized to the physical therapy group ( $n=56$ ) received transcutaneous electrical nerve stimulation and infrared thermotherapy, while those in the aquatic group (57) received aquatic exercise. The primary outcome measure, completed both before and after treatment, was the 34-item Roland Morris Disability Questionnaire (RMDQ). Outcome measures included pain on an 11-point numeric rating scale (NRS).

Compared to those in the physical therapy group, those in the aquatic group showed improvement in RMDQ scores by -1.77 points after the three-month intervention, -2.42 points at six months, and -3.61 points at 12-months. Scores on the NRS for the most severe pain were less in the aquatic group at three ( $p=0.006$ ), six ( $p=0.006$ ), and at 12 months ( $p=0.001$ ).

**Conclusion:** This study of patients with chronic low back pain found that aquatic therapy provided

better improvement than did physical therapy using transcutaneous electrical nerve stimulation and infrared thermotherapy.

Peng, M., et al. Efficacy of Therapeutic Aquatic Exercise vs Physical Therapy Modalities for Patients with Chronic Low Back Pain: A Randomized Clinical Trial. *JAMA Netw Open.* 5(1), e2142069. <https://doi.org/10.1001/jamanetworkopen.2021.42069>, 2022; 5(1):e2142069.

## TAI CHI NEUROCOGNITIVE FUNCTION AND MORTALITY

Tai Chi (TC) is a martial art involving low-impact movement, balance, and mental concentration. Several studies have demonstrated a benefit of TC for reducing falls and improving physical function. This study examined the effect of TC participation on physical and neurocognitive functions, frailty, quality of life, and mortality.

Data were analyzed from two combined population cohorts ( $n=6,074$ ) in the Singapore Longitudinal Aging Study (SLAS),  $\geq 55$  years of age at baseline. At baseline, the participants were asked the frequency with which they engaged in TC, brisk walking, or other active sports. Other measures included the Nutrition Screening Initiative (NSI), Knee Extension Strength, Gait Speed, Timed-Up-and-Go (TUG) and Performance-Oriented Mobility Assessment (POMA). A neurocognitive test battery was completed on a random selection of participants.

Compared to those with infrequent TC participation (I-TC), which included those who scored as never participated (5,324) or participated less than once per week ( $n=83$ ), frequent TC (F-TC) participants ( $n=572$ ) had a reduced likelihood of impaired physical quality of life ( $p<0.001$ ) and reduced mortality ( $p<0.001$ ). At follow-up, the physical function composite index increased in the F-TC group, but not

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in the I-TC group ( $p < 0.001$ ). In addition, the F-TC group displayed a decreased incidence of prefrailty (Odds Ratio 0.4), and increased levels of attention and working memory (Digit Span Forward;  $p = 0.003$ ), visual-motor tracking and mental flexibility (Trial making tests A/B;  $p = 0.008$ ) performances, and better verbal learning and memory (RAVLT-Delayed Recall) compared to the I-TC group.

**Conclusion:** This large population study found that the practice of Tai Chi at least once per week was associated with improved cognitive function and reduced frailty.

Lee, S., et al. Association of Tai Chi Exercise with Physical and Neurocognitive Functions, Frailty, Quality of Life and Mortality in Older Adults: Singapore Longitudinal Ageing Study. *Age and Ageing*. 2022, April; 51(4): 1–6.

### **ATRIAL FIBRILLATION AND ACCELERATION OF FRAILTY**

The prevalence of atrial fibrillation (AF) increases with age. As frailty is an age-associated condition characterized by reduced physiological reserve, greater vulnerability to stressors and increased risk of morbidity and mortality, this study was designed to better understand the relationship between AF and incident frailty. Data were retrieved from the Longitudinal Study on Ageing (TILDA) to investigate whether older adults living with AF were more likely to develop frailty than age matched controls.

This Irish study included community-dwelling adults  $\geq 50$  years of age with baseline data (Wave one) collected between October 2009 and February 2011. Subsequent data were collected through 2018. A comprehensive health assessment at Wave one included an ECG. The persistence of AF was assessed by cross-referencing participants' ECGs at Waves one and three for the presence of AF. Frailty was identified at each wave using a phenotype-based model, using five characteristics: unexplained weight loss, exhaustion, low grip strength, low walking speed, and low physical activity. Cognition was assessed using the Mini-Mental State Examination. One hundred eighteen subjects with AF at Wave one were matched to 236 controls.

At Wave one, compared to the control group, the AF group had a greater percentage of frail participants (7.5% vs 20.3%) as well

as a greater percentage of pre-frail participants (28.1% vs 39.2%;  $p < 0.001$ ). This relationship persisted at Wave Five.

**Conclusion:** This Irish longitudinal study of community-dwelling adults found that atrial fibrillation may be associated with an acceleration of frailty.

Richard, G., et al. Atrial Fibrillation and Acceleration of Frailty: Findings from the Irish Longitudinal Study on Ageing. *Age Ageing*. 2022 Feb; 51(2):afab273. doi: 10.1093/ageing/afab273.

### **BLOOD FLOW RESTRICTION VERSUS HIGH LOAD RESISTANCE AND PATELLA TENDON PROPERTIES**

Recent data has suggested that similar muscle adaptations occur when training with low load resistance with blood flow restriction (LL-BFR) and high load (HL) resistance training. As little data exists concerning the tendon adaptations during LL-BFR training, this study compares the differences between these two training methods in producing patella tendon adaptations.

Subjects were sedentary adults 18-40 years of age. The group was randomized to undergo three, one-hour sessions per week, for 14 weeks of training (bilateral leg press, knee extension, and standing and sitting calf raises) with either HL [70-85% one recognition maximum (1RM)] or LL-BFR (20-35% 1RM). Before and after training all subjects underwent an assessment of the patella tendon mechanical properties using b-mode ultrasound, MRI assessment of the patella tendon and quadriceps muscle cross-sectional area. The 1RM of the quadriceps was reassessed every four weeks.

No significant differences were found between the groups in measures of patella tendon stiffness, rectus femoris cross-sectional, and improvement in the 1RM during the leg press. Greater gains in knee extension strength were noted in the LL-BFR group ( $p = 0.044$ ).

**Conclusion:** This study of untrained adults found that both low-load blood flow restricted exercise and high-load resistance training resulted in comparable changes in patella tendon stiffness, patella tendon cross-sectional area, and muscle mass. Knee extension strength gains were greater in the LL-BFR group.

Centner, C., et al. Low Load Blood Flow Restriction and High Load Resistance Training Induce Comparable Changes in Patellar Tendon Properties. **Med Sci Sports Exerc.** 2022. Published ahead of print. DOI: 10.1249/MSS.0000000000002824.

### MILD COGNITIVE IMPAIRMENT AND DEMENTIA IN FORMER PROFESSIONAL FOOTBALL PLAYERS

Mild cognitive impairment (MCI) affects a substantial proportion of Americans with the cumulative risk of conversion to dementia-related conditions estimated to be 24–32%. As the overall prevalence of Alzheimer's disease in former National Football League (NFL) players appears to be higher than that of the general population, this study assessed the incidence of MCI among former professional football players.

Former NFL players of all ages were contacted, with 1,784 responding. Of these, 922 who were ≥50 years of age, were chosen for participation. The subjects completed a questionnaire that queried personal demographics, football-playing history, medical history, concussion history as well as current psychological physical, and cognitive functioning. Participants were asked if a medical provider had diagnosed them as having MCI, Alzheimer's disease, frontal temporal dementia, Lewy body dementia, vascular dementia, or other dementia. These were combined as "dementia" for the analysis.

A diagnosis of dementia was more frequent in older age groups than among those who were younger. Among those 50 years of age or older, a self-reported diagnosis of MCI was found in almost ¼ of the participants. Compared to those reporting no concussions, those with a lifetime history of ten or more concussions had a higher prevalence of self-reported MCI and dementia (prevalence ratio (PR) 1.66 and 2.61, respectively). A greater risk of MCI or dementia was also noted among those with depression (PR 2.70 and 3.22, respectively), anxiety (PR 1.96 and 3.14, respectively), sleep apnea (PR 1.13 and 1.42, respectively), and recent pain intensity (PR 1.13 and 1.15 respectively).

**Conclusion:** This study of former national football league players ≥50 years of age found that 23% reported a diagnosis of MCI, with an increased prevalence among those with more

than 10 concussions, diagnoses of depression, anxiety, severe pain, or sleep apnea.

Walton, S., et al. Mild Cognitive Impairment and Dementia Reported by Former Professional Football Players over 50 Years of Age: An NFL-Long Study. **Med Sci Sport Exerc.** 2022, March 1;54(3): 424-431.

### ACUTE ACTIVITY AND CONCUSSION RECOVERY

In 2001, the First International Conference on Concussion in Sport, released the first Concussion in Sport (CIS) Consensus Statement. This document recommended that patients with a concussion be treated with rest and no activity until asymptomatic. Both the fifth CIS and the Centers for Disease Control and Prevention continue to recommend cognitive and physical rest for up to 48 hours before initiating symptom limiting activities. These recommendations have been based on limited evidence. This study compared the timing and level of physical and mental activity in the first 48 hours after concussion with the time to symptom-free status.

Subjects were 78 collegiate athletes who experienced a sports-related concussion that resolved within two months. All had completed the Sport Concussion Assessment Tool (SCAT) during a baseline/preparticipation assessment. The athlete was assessed daily with the SCAT, and then twice per week with the ImPACT until baseline values were achieved. The two predictors in the study were daily five-point (0-5) self-reported physical activity and self-reported mental activity.

Using a quadratic regression, early physical activity was a significant predictor for shorter symptom-free days ( $p=0.002$ ) and return to play ( $p=0.006$ ). Early mental activity did not predict either time to symptom-free or return to play.

**Conclusion:** This study found that mild-to-moderate physical activity immediately after concussion was associated with a reduced time to symptom-free and reduced time to return to play. No association was found between mental activity and symptom resolution or return to play.

Buckley, T., et al. Acute Physical and Mental Activity Influence on Concussion Recovery. **Med Sci Sport Exerc.** 2022, February;54(2): 307–312.

### PHYSICAL FITNESS AND COGNITIVE PERFORMANCE IN PRESCHOOL CHILDREN

An increasing number of children experience physical activity levels below current recommendations. Previous studies have demonstrated associations between physical fitness and cognitive performance as well as the impact of physical exercise programs on cognitive performance. This study explores the relationship between individual elements of physical fitness and variance in measures of attention.

Subjects included 61 children ages 4-6 years of age located in three kindergartens in eastern Germany. Children were tested for static balance, strength, power, and coordination. These were tested with a single leg stance test, long jump test, handgrip strength test, and hopping on one leg test. Attention was measured with the Konzentrations-Handlungsverfahren für Vorschulkinder test.

The composite score of physical fitness was positively associated with the composite score of attention before and after adjusting for age, body height, and body mass ( $p < 0.05$ ). A stepwise multiple linear regression analysis found a positive association between coordination (hopping on one leg) and the composite score of attention ( $p < 0.01$ ).

**Conclusion:** This study of preschool children found that higher performance in physical fitness, especially balance, is related to better attentional capacity.

Wick, K., et al. Associations between Measures of Physical Fitness and Cognitive Performance in Preschool Children. **BMC Sports Sci Med Rehabil.** 2022, May 1. 14(1):80.

### MUSCLE STRENGTH AND PHYSICAL PERFORMANCE IMPROVE FRACTURE RISK PREDICTION

Approximately 79% of fractures occur in men without a verified diagnosis of osteoporosis. The Garvan fracture risk calculator (Garvan) and the Fracture Risk Assessment Tool (FRAX) are among the most commonly used tools to estimate absolute fracture risk. This study assessed the role of muscle strength and physical performance in fracture risk prediction over and above these two tools.

This prospective cohort study included community-dwelling men, ≥

65 years of age, enrolled between March 2000 and April 2002. Baseline data included grip strength and functional performance (gait speed and chair stands), as well as risk factors included in the Garvan and FRAX algorithms. Fractures were reported through a questionnaire every four months and categorized as any fracture (fracture sites excluding skull, finger, and toe), major osteoporotic fracture (MOF), including hip, proximal humerus, wrist, and clinical vertebral fractures, initial hip (IH), including hip fractures not preceded by other fractures, any hip fracture (AH), including all hip fractures, even if preceded by other fractures.

Data were completed for 5,665 men with a mean age of 73.5 years, at a median follow-up of 12.7 years. During follow-up, 18% sustained at least one low trauma fracture. Gait speed was lower among those who sustained MOFs or hip fractures but not in those who sustained any fracture. Worse grip strength and physical performance were associated with increased A, MOF, IH, and AH fracture risk, over and above the established risk factors.

**Conclusion:** This study found that adding muscle strength and performance measurements to the traditional risk prediction tools, Garvan and FRAX, improved fracture risk prediction.

Alajlouni, D., et al., Muscle Strength and Physical Performance Improve Fracture Risk Prediction Beyond Garvan and FRAX: The Osteoporotic Fractures in Men (MrOS) Study. *J Bone Miner Res.* 2022; 37(3): 411-419.

### **HYPERBARIC OXYGEN, MITOCHONDRIAL RESPIRATION, AND PERFORMANCE IN MIDDLE AGE**

Research has shown that maximal aerobic fitness, evaluated by measuring the maximal oxygen capacity ( $VO_{2max}$ ) and anaerobic threshold (AT), strongly correlate with skeletal muscle mitochondria content (mitochondrial quantity) and skeletal muscle respiratory capacity. This study evaluated the effect of hyperbaric oxygen therapy (HBOT) on maximal physical performance and mitochondrial function in middle-aged master athletes.

This double-blind randomized placebo-controlled trial included 37 master athletes 40-50 years of age. The subjects were randomly assigned to a sham or an HBOT group, to

engage in daily sessions, five days per week for two months. At baseline and follow up the subjects were assessed with pulmonary function tests, and a cardiopulmonary maximal exercise test to determine maximal power output, maximal oxygen consumption ( $VO_{2max}$ ), anaerobic oxygen consumption ( $VO_{2AT}$ ), breathing reserve (BR), RER, heart rate, minute ventilation ( $V_E$ ), volume of  $CO_2$  expired ( $VCO_2$ ), and mitochondrial respiration using muscle samples from the gluteus maximus.

Compared to the sham group, the HBOT group demonstrated significantly better improvement in  $VO_{2max}$  ( $p=0.01$ ),  $VO_{2AT}$  ( $p=0.026$ ), and  $VO_2$ /kilogram ( $p=0.03$ ). In addition, compared to the sham group the HBOT group mitochondria were found to have significantly greater increases in maximal coupling capacity ( $p=0.04$ ), maximal uncoupled capacity ( $p = 0.02$ ), mitochondrial complex I function ( $p=0.01$ ), and mitochondrial mass markers ( $p=0.002$ ).

**Conclusion:** This study of 37 athletes, 40-50 years of age found that hyperbaric oxygen therapy could improve mitochondrial respiration.

Hadanny, A., et al. Effects of Hyperbaric Oxygen Therapy on Mitochondrial Respiration and Physical Performance in Middle-Aged Athletes: A Blinded, Randomized Controlled Trial. *Sports Med Open.* 2022. 8:22.

### **TWENTY-FOUR-HOUR MOVEMENT AND COGNITION IN THE ELDERLY**

Sedentary behavior is a modifiable risk factor associated with numerous poor health outcomes and mortality. Using new accelerometer technology, the National Health and Nutrition Examination Survey (NHANES) deployed a 24-hour continuous monitoring protocol to quantify total continuous movement within a 24-hour period. This study examined how this movement parameter would correlate with cognitive function among adults 60 years of age and older.

The NHANES is a sample of institutionalized adults in the United States. In the 2011 through 2014 cycles participants were invited to wear a physical activity monitor for seven consecutive days. The continuous movement percentile was used to categorize participants into quartiles. A multivariable linear regression model was used to investigate the association between

movement quartiles and cognitive scores using a series of cognitive assessments.

Data were obtained from 2,518 participants who completed all cognitive tests. Compared to the lowest quartile, those in higher movement quartiles had better memory performance, language/verbal fluency, and executive performance. Compared to the lowest quartile, those in the highest quartile movement were associated with a lower odds of reporting difficulties with memory (HR .57) in thinking or remembering (HR .49).

**Conclusion:** Using data from the NHANES trial researchers found a direct association between the percentage of a 24-hour period in which the individual was moving, and higher cognitive functioning.

Dooley, E., et al. Higher 24-Hour Total Movement Activity Percentile is Associated with Better Cognitive Performance in US Older Adults. *Med Sci Sports Exerc.* 2022. Published ahead of print.

### **BURST SPINAL CORD STIMULATION FOR CHRONIC INTRACTABLE PAIN**

Spinal cord stimulation (SCS) has been used as a treatment option for patients with intractable neuropathic pain of the trunk and/or extremities. In the past decade, the technique of passive recharge burst spinal cord stimulation (B-SCS) has been introduced as an alternative to conventional tonic SCS (t-SCS). This study evaluated the long-term efficacy of this technique.

This prospective, single-arm study enrolled 269 participants with chronic, intractable pain of the trunk, and/or lower limbs, who reported Numeric Rating Scale (NRS) pain scores of at least 6/10. The B-SCS device was programmed with both tonic and burst settings. Outcomes were evaluated at regular intervals up to 24 months, using questionnaires regarding pain intensity, patient-reported pain relief, quality of life (EG-5D), mood and affect (Pain Catastrophizing Scale), State-Trait Anxiety Inventory, PHQ-9, a fear-avoidance scale, sleep scale, and physical function.

Of the 269 subjects enrolled 128 completed the 24-month study. Compared to baseline scores, the NRS scores of the treatment group improved by 60.3% at six months, 63.1% at 12 months, and 60% at 24 months. Health-related quality of life was significantly improved across all domains at 24 months. Reduced

opioid use was reported by 48% of the subjects. At 24 months 84.4% declared that they were satisfied or very satisfied with the results.

**Conclusion:** This study of adults with chronic intractable back and limb pain found that a spine stimulator using passive recharge burst spinal cord stimulation (B-SCS) could produce long-term improvement in physical, mental, and emotional functioning.

Deer, T., et al. Passive Recharge Burst Spinal Cord Stimulation Provides Sustainable Improvements in Pain and Psychosocial Function: 2-year Results from the TRIUMPH Study. *Spine*. 2022, Apr 1;47(7):548-556.

### MICROBIOME AND BONE DENSITY

Animal studies have shown that skeletal homeostasis can be affected by the gut microbiome. However, there are very few studies in humans that examine the associations between the gut microbiome and skeletal status. This study explored the association between the fecal microbiome with measures of bone density, microarchitecture, and strength in older men.

Subjects were community-dwelling men 78-98 years of age participating in the Osteoporotic Fractures in Men (MrOS) study—a longitudinal observational study of musculoskeletal health and aging. Stool samples were obtained for rRNA sequencing. The bone measures were obtained with high-resolution peripheral quantitative computed tomography (HRpQCT) and DXA. The stool samples were then assigned a taxonomy. The microbiome components were then compared to measures of bone health.

Four genera were associated with skeletal measures. A greater *Anaerofilum* abundance was associated with lower radial and tibial density, radial and tibial strength, tibial cortical thickness and cortical porosity, and hip DXA BMD. *Methanomassiliicoccus* was associated with greater distal tibial cortical porosity. A greater abundance of *Ruminiclostridium* 9 was associated with less distal tibial cortical porosity, while a greater abundance of *Tyzzarella* was associated with greater tibial density measures.

**Conclusion:** This large study of elderly men found an association between bone architecture and four

genera found in the fecal microbiome (*Anaerofilum*, *Methanomassiliicoccus*, *Ruminiclostridium* 9, and *Tyzzarella*).

Orwoll, E., et al. Analysis of the Associations between the Human Fecal Microbiome and Bone Density, Structure and Strength: The Osteoporotic Fractures in Men (MrOS) Cohort. *J Bone Miner Research*. 2022, April; 37(4) April:597–607.

### NEW SUSTAINED-RELEASE PREGABALIN FOR PERIPHERAL NEUROPATHY

Peripheral neuropathic pain is caused by a lesion or disease of the peripheral somatosensory nervous system, with a broad range of underlying etiologies. This study assessed the efficacy of a new once-daily sustained-release pregabalin formula, compared to a twice-daily immediate-release formula.

This phase three, double blind, active-control study included adults 19-79 years of age with a diagnosis of painful diabetic peripheral neuropathy (DPN) or peripheral herpetic neuropathy (PHN). The subjects were randomly assigned to receive 12 weeks of once-daily SR pregabalin 150mg, or twice per day instant release pregabalin 150 mg. After one week the dose was increased to 300mg and then as needed, titrated to 600mg. The primary outcome was pain, as measured by the Daily Pain Rating Scale (DPRS).

Data were completed for 319 patients including 154 in the SR and 165 in the IR group. The mean DPRS scores in both treatment groups decreased significantly from baseline at all visits ( $p < 0.0001$  for all comparisons). The DPRS scores between groups were not significant at any time point.

**Conclusion:** This study found that a new sustained-release (SR) pregabalin formulation is non-inferior to immediate-release (IR) pregabalin for relieving peripheral neuropathic pain.

Han, K., et al. Efficacy and Safety of a New Sustained-release Pregabalin Formulation Compared with Immediate-release Pregabalin in Patients with Peripheral Neuropathic Pain: A Randomized Noninferiority Phase 3 Trial. *Clin J Pain*. 2022, May; 38(5) 343-350.

### TRANSCRANIAL ALTERNATING CURRENT STIMULATION AND VISUAL PERCEPTUAL LEARNING

Repetitive visual experience or practice results in a dramatic and long-lasting improvement in perceiving visual content. This is referred to as visual perceptual learning (VPL). As transcranial alternating current stimulation (tACS) has been used to enhance neuroplasticity for several medical conditions this study assessed the efficacy of tACS for the improvement of VPL.

This exploratory study involved 121 healthy adult subjects, assigned to one of six groups. While practicing an orientation discrimination task, the subjects received occipital stimulation of their visual cortex using tACS at a given frequency (6, 10, 20, or 40 Hz), sham tACS, or bilateral sensorimotor tACS at 10Hz. Stimulation was delivered, with a peak-to-peak intensity of 1.5 mA. The primary outcome was the difference between groups on the discrimination task.

The subjects' orientation discrimination thresholds improved with training for all of the training groups. The improvement in the orientation task was greater in the 10 Hz occipital stimulation group than in the other stimulation groups ( $p < 0.001$  for all comparisons). Compared with the sham occipital stimulation group, only the 10Hz group showed faster and greater learning. The subjects were retested 14 months later with no significant loss in the discrimination thresholds of the 10 Hz occipital stimulation group, demonstrating long-lasting learning.

**Conclusion:** This study found that occipital transcranial alternating current stimulation at 10 Hz accelerated visual perceptual learning.

He, Q., et al. Boosting Visual Perceptual Learning by Transcranial Alternating Current Stimulation over the Visual Cortex at Alpha Frequency. *Brain Stimul*. 2022, May-June; 15 (3):546-553.

### CANNABIDIOL EFFECTS ON EXERCISE PHYSIOLOGY AND BIOENERGENICS

Cannabidiol (CBD) is a non-intoxicating plant-derived cannabinoid, recently approved by the Food and Drug Administration of the US for the treatment of intractable pediatric epilepsy. This study explored the effects of acute, oral CBD on physiological and

psychological responses to submaximal and exhaustive running exercise.

The nine subjects were endurance-trained males who underwent two baseline treadmill assessments. For Run 1, the subjects ran for 60 minutes at a fixed intensity (70%  $VO_{2max}$ ). Run 2, beginning 30 minutes after completing Run 1, was completed at a fixed speed (10 km · h<sup>-1</sup>) with increasing treadmill angles, until volitional exhaustion. The subjects then completed two testing sessions, randomly assigned to receive either a placebo or CBD 300mg before Run 1. The CBD and placebo conditions were compared for differences in physiologic and subjective outcomes, using a standardized mean difference of each measure against the standard deviation of change. The results were interpreted as “uncertain”, “unlikely affected” or “possibly affected” with the latter interpreted as positive and worthy of follow-up investigation.

During Run 1 the effects of CBD on  $VO_2$ , blood lactate, and subjective pleasure were “possibly affected”. During Run 2 the effects of CBD on  $VO_{2max}$ ,  $VCO_{2max}$  and maximum respiratory exchange ratio were “possibly affected”. All other parameters were rated as “uncertain” or “unlikely”.

**Conclusion:** This study of adult males engaged in aerobic exercise suggests that CBD does not seem to alter performance variables but may improve several key parameters, including submaximal and maximal oxygen consumption and feelings of pleasure.

Sahinovic, A., et al., Effects of Cannabidiol on Exercise Physiology and Bioenergetics: A Randomized Controlled Pilot Trial. **Sports Med-Open.** 8(1), 27. <https://doi.org/10.1186/s40798-022-00417-y>.

### REGIONAL ANESTHESIA AND POSTOPERATIVE DELIRIUM

Among patients 65 years of age or older, delirium after hip fracture surgery can be a source of significant morbidity. This study compared the postoperative delirium incidence between patients treated with general anesthesia to those treated with regional anesthesia.

Subjects were 950 patients, 65-80 years of age with a fragility hip fracture, scheduled for surgical repair. All were assessed pre-surgically for delirium using the Confusion Assessment Method (CAM). Cognitive function was measured by

the Mini-Mental State Exam (MMSE). Patients were randomized to receive either general anesthesia or regional anesthesia. The primary outcome was the number of patients experiencing 1-2 occasions of postoperative delirium during the first week after surgery.

Postoperative delirium was experienced on one or more occasions by 29 (6.2%) of the regional anesthesia group and 24 (5.1%) in the general anesthesia group. Multiple episodes occurred in 2.8% of the regional anesthesia group and 3.0% of the general anesthesia group. All-cause 30-day mortality rate was 1.7% in the regional anesthesia group and 0.9% in the general anesthesia group.

**Conclusion:** This study of elderly patients undergoing hip fracture repair found no difference in the rate of postoperative delirium between those receiving general and those receiving regional anesthesia

Li, T., et al. Effect of Regional Vs General Anesthesia on Incidence of Postoperative Delirium in Older Patients Undergoing Hip Fracture Surgery: The RAGA Randomized Trial. **JAMA.** 2022, January; 327(1):50–8.

### OBESITY AMONG PATIENTS UNDERGOING TOTAL KNEE ARTHROPLASTY 2013-2020

The Center for Disease Control and Prevention has reported that the rates of obesity in the United States have risen from 30.5% in 1999 to 42.4% in 2018. This study assessed the trends in body mass index (BMI) among patients who underwent total knee arthroplasty (TKA) at a large urban center.

This retrospective analysis included data from patients undergoing primary TKA from 2013 to 2020. The BMI categories included underweight (BMI, <18.5 kg/m<sup>2</sup>), obese (BMI, >30 kg/m<sup>2</sup>), Class-I obesity (BMI, 30 to 34.9 kg/m<sup>2</sup>), Class-II obesity (BMI, 35 to 39.9 kg/m<sup>2</sup>), and Class-III obesity (BMI, >40 kg/m<sup>2</sup>). The primary outcome was the yearly trends comparing patients undergoing primary TKA and those in the general population.

Data were included for 11,333 patients undergoing primary TKA and 1,158,168 patients undergoing an annual physical examination (control group). The mean BMI for the TKA group was significantly greater (p < 0.001) every year compared with the control group. The mean BMI for the control group increased from 25.40 ±

5.40 kg/m<sup>2</sup> in 2013 to 27.66 ± 6.15 kg/m<sup>2</sup> in 2020 (p<0.001), but remained relatively stable in the TKA group, moving from 32.39 kg/m<sup>2</sup> in 2013 to 32.71 kg/m<sup>2</sup> in 2020.

**Conclusion:** This study of patients seen in a large medical practice group found that, while the average BMI increased significantly from 2013 to 2020, the mean BMI among those undergoing knee joint replacement remained relatively stable.

Muthusamy, N et al., Trends of Obesity Rates Between Patients Undergoing Primary Total Knee Arthroplasty on the General Population from 2013-2020. **J Bone Joint Surg Am.** 2022, March 16;104(6):537-543.

### AZD7442 TO PREVENT COVID-19

AZD7442 is a combination of two fully human, SARS-CoV-2–neutralizing monoclonal antibodies, derived from antibodies isolated from B cells obtained from persons infected with Covid-19. This study evaluated the efficacy of AZD7442 for the prevention of symptomatic and severe Covid-19.

This ongoing, multicentered, double-blind, randomized, placebo-controlled trial included adults 18 years of age or older with an increased risk of an inadequate response to vaccination against Covid-19, an increased risk of exposure to Covid-19 or both. The subjects were randomized to receive a single 300-mg dose of AZD7442 (one 1.5-ml intramuscular injection of each antibody administered consecutively) or saline placebo (two 1.5-ml intramuscular injections administered consecutively) on day one. The primary efficacy end point was symptomatic and confirmed Covid-19 infection on or before day 183.

Subjects were 5,197 in the active treatment group and 1,737 in the placebo group. By day 183, symptomatic Covid-19 had occurred in 0.2% in the treatment group and 1.0% in the placebo group (p<0.001). Five severe cases including two deaths occurred in the placebo group, with no deaths in the treatment group. Adverse events did not differ between the groups.

**Conclusion:** This study of adults with an increased risk of a poor response to a Covid-19 vaccine found that a single injection of AZD7442 could significantly reduce the risk of symptomatic and severe COVID-19.

Levin, M., et al. Intramuscular AZD7442 (Tixagevimab– Cilgavimab) for Prevention of Covid-19. *N Eng J Med.* 2022, April. DOI: 10.1056/NEJMoa2116620.

### DARIDOREXANT FOR INSOMNIA DISORDER

Those with insomnia report a wide range of daytime complaints including reduced energy, fatigue, and mood disorders. No studies involving sleep medications have demonstrated an improvement in daytime symptoms. This study was designed to assess the efficacy of the dual orexin receptor antagonist, daridorexant, to treat insomnia and the associated daytime symptoms.

Two multicenter randomized double-blind placebo-controlled parallel-group trials were completed involving adults with a diagnosis of insomnia disorder. Combined, the studies involved patients in 156 hospitals and sleep centers randomized to receive placebo or daridorexant 10 mg, 25 mg, or 50 mg. Subjects completed twice daily diary entries documenting visual analog scales, wake time after sleep onset (WASO), self-reported total sleep time, and the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ). The primary endpoints were the change from baseline in WASO and latency to persistent sleep (LPS), measured by polysomnography, at baseline, and then one and three months.

In study one, compared to the placebo group, greater improvements were found in the daridorexant 50 mg group in LPS scores, the total sleep time, and the WASO at one and three months ( $p < 0.0001$  for all comparisons). Greater improvements were also noted in the daridorexant 25mg group for the WASO, LPS, and self-reported sleep times ( $p = 0.015$ - $p < 0.0001$ ). In study two, compared to placebo, better scores were found in the WASO and self-reported sleep times at one and three months ( $p < 0.0001$  and  $p = 0.028$  respectively).

**Conclusion:** This study of patients with insomnia disorder found that daridorexant at 25 mg and 50 mg improved sleep outcomes while the 50 mg group also had improvement in daytime functioning.

Mignot, E., et al. Safety and Efficacy of Daridorexant in Patients with Insomnia Disorder: Results from Two Multicentre Randomized Double-Blind, Placebo-Controlled, Phase Three Trials. *Lancet Neurol.* 2022, February; 21(2):125-139.

### ORAL TEBIPENEM PIVOXIL FOR COMPLICATED URINARY TRACT INFECTION

As antimicrobial resistance escalates, worldwide multidrug-resistant gram-negative uropathogens have increased in frequency among hospitalized patients. This international phase three trial evaluated the efficacy of oral tebipenem pivoxil hydrobromide in hospitalized patients with complicated urinary tract infection (UTI) or acute pyelonephritis.

This phase three, randomized, double-blind study included hospitalized adult patients with a diagnosis of complicated UTI or acute pyelonephritis. The subjects were randomized to receive 7-10 days of either oral tebipenem pivoxil hydrobromide 600 mg every eight hours plus a placebo infusion every 24 hours, or one gram IV ertapenem every 24 hours plus a placebo tablet every eight hours. The primary efficacy endpoint was the overall response (a composite of clinical cure and favorable microbiologic response) on day 19 in the intention-to-treat population. Clinical cure was defined as complete resolution or clinically significant alleviation of baseline signs and symptoms. The noninferiority margin was set at 12.5%.

Data were available for 868 patients, of whom 50.8% had complicated UTIs and 49.2% had acute pyelonephritis. Clinical cure on day 19 was observed in 93.1% of the pivoxil and 93.6% of the ertapenem patients. The primary endpoint was achieved in 58.8% of the pivoxil and 61.1% of the ertapenem group. Adverse events were observed in 25.7% of the pivoxil and 25.6% of the ertapenem group, with the most common being mild diarrhea and headache.

**Conclusion:** This study found that oral tebipenem pivoxil hydrobromide was non-inferior to intravenous ertapenem for the treatment of complicated urinary tract infection and acute pyelonephritis.

Eckburg, P., et al., Oral Tebipenem Pivoxil Hydrobromide in Complicated Urinary Tract Infection. *N Eng J Med.* 2022, April 7 ;386:1327-1338.

### REVISION AFTER TOTAL HIP ARTHROPLASTY UNDER 50 YEARS

It has been estimated that by the year 2030, 52% of primary total hip arthroplasties in the US will be for

patients <65 years of age. This study explored the outcome of THAs and subsequent revision procedures in patients < 50 years of age.

This retrospective cohort study included all patients undergoing a primary THA between January 1988 and December 31, 2022. During that time 1,049 primary THAs were performed in 860 patients under the age of 50 years. The survival of the primary THA was recorded as the time between the primary procedure and the date of revision, death of the patient, or date of the most recent outpatient review. The results were stratified for sex, age group, and different primary indications.

The survival rates of all primary THAs were 66.7% at 20-year follow-up and 54.4% at 25-year follow-up. The 138 revisions were performed at a mean age of 48.2 years.

**Conclusion:** This study of patients <50 years of age who underwent total hip arthroplasty found that 66% of the joints survived to 20-years.

Kuijpers, M., et al. The Outcome of Subsequent Revisions After Primary Total Hip Arthroplasty In 1,049 Patients Aged Under 50 Years: A Single-Centre Cohort Study with a Follow-Up of More Than 30 Years. *Bone Joint J.* 2022; 104-B (3):368-375.

### RETINAL PHOTOGRAPH-BASED LEARNING PREDICTS AGE, MORBIDITY AND MORTALITY

Globally, the number of persons aged 80 years or over is projected to increase more than threefold between 2017 and 2050, reaching 425 million in 2050. This study investigated the efficacy of a retina-based marker of biologic age (BA) in the risk stratification of mortality and morbidity.

The authors trained a deep learning (DL) algorithm using data from the Korean Health Screening study to predict the probability of age being  $\geq 65$  years ('RetiAGE'). In this process, the authors sought patterns in the retina related to age by comparing an 'older' group with a 'younger' group in a broad and unspecific way. This was done with age cutoffs of 65, 70, and 75 years. In addition, a PhenoAGE phenotype was created using demographic and clinical data, including chronologic age, albumin, creatinine, glucose, c-reactive protein (log), lymphocyte percent, mean (red) cell volume, red cell distribution width, alkaline phosphatase, and white blood cell

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count. Data were reviewed to estimate the hazard ratios (HRs) corresponding to the associations between RetiAGE and the five outcomes

Over a 10-year follow-up of the 46,551 participants, 2,236 (4.0%) died. Using a grading system based on RetinAge, compared to those in the first quartile, those in the fourth quartile had a higher risk of mortality (HR=1.67), a higher risk of CVD mortality (HR=2.42), and a higher risk of cancer mortality (HR=1.60). Also, compared with the first quartile group, the risk of CVD and cancer morbidity in the fourth quartile group increased by 39% (HR=1.39 [1.14–1.69]) and 18% (HR=1.18 [1.10–1.26]), respectively.

**Conclusion:** This study demonstrates that retinal photographs could be used to stratify the risk of mortality and morbidity due to vascular and cancer-related diseases.

Nusinovici, S., et al. Retinal Photograph-Based Deep Learning Predicts Biological Age and Stratifies Morbidity and Mortality Risk. *Age Ageing*.2022, April;51:1-9.

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