

# REHAB IN REVIEW

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## ACUPUNCTURE FOR INSOMNIA

Insomnia is the most frequently encountered sleep disturbance in medical practice. As acupuncture has been used to treat primary insomnia in China for generations, this literature review and meta-analysis was designed to better understand the efficacy of this ancient intervention.

A literature review was conducted for studies involving acupuncture for insomnia. The search criteria included randomized, controlled trials involving patients diagnosed with primary insomnia and treated with traditional needle acupuncture. The primary outcome variables were objective sleep parameters. Secondary outcomes included subjective reports of sleep quality.

Data were analyzed from 11 studies including a total of 775 patients with primary insomnia. Of these, 418 received verum acupuncture and 357 received sham/placebo acupuncture. The meta-regression analysis found that verum-acupuncture increased total sleep time ( $p < 0.01$ ) and sleep efficiency ( $p < 0.01$ ), reduced awakening after sleep onset ( $p < 0.01$ ) and decreased the number of awakenings after sleep onset ( $p < 0.01$ ). In 10 of 11 trials (90.91%), when objective sleep parameters improved, the patient's self-reported scores also improved.

**Conclusion:** This literature review and meta-analysis found that acupuncture can improve objective and subjective sleep parameters.

Zhao, F., et al. Can Acupuncture Improve Objective Sleep Indices in Patients with Primary Insomnia? A Systematic Review and Meta-analysis. *Sleep Med.* 2021, April; 80: 244-259.

## TRENDS IN DEMENTIA IN THE UNITED STATES

Previous studies have suggested that the risk of dementia is higher in non-Hispanic Black (NH-B) than in non-Hispanic White individuals (NH-

W). This study evaluated the relative racial disparities in dementia between the years 2000 and 2016.

Data were obtained from the United States Health and Retirement Study (HRS). Every two years the wave of HRS interviews included the collection of data on sociodemographic characteristics, cognitive and physical function, health status, and social engagement. The authors used each wave as its own cross-sectional study to quantify racial disparities in the prevalence of dementia at 2-year intervals from 2000 through 2016.

On average, across all years, 20% of participants were classified as having dementia, resulting in a crude dementia rate of 6.3 cases per 100 person-years. While the overall prevalence of dementia declined with time, NH-B participants had an approximately 1.4 to 1.8 times higher incidence of dementia compared to NH-W. The NH-B group had a slight decline in the crude prevalence ratio comparing NH-B with NH-W participants in later years, though this did not reach statistical significance.

**Conclusion:** This study, using a representative sample of U.S. citizens, found that, while the overall incidence of dementia is falling, the relative ratio of dementia between NH-B and NH-W individuals remained constant between the years 2000 and 2016.

Power, M., et al. Trends in Relative Incidence and Prevalence of Dementia across Non-Hispanic Black and White Individuals in the United States, 2000-2016. *JAMA Neurol.* 2021, March; 78(3): 275-284.

## ZINC AND INTRACRANIAL ANEURYSM

Intracranial aneurysm (IA) is the main cause of subarachnoid hemorrhage. The mechanism of initiation, progression, and rupture of these aneurysms remains largely unclear. Studies have shown that IAs are associated with nuclear factor  $\kappa$ B (NF- $\kappa$ B)-dependent inflammation in

cerebral arterial walls. As zinc supplementation can decrease the activation of NF- $\kappa$ B, this study assessed whether zinc can also prevent the growth of experimental IAs.

Seven-week-old male rats were separated into three groups. These included a control, a vehicle-treated group (V), and a zinc-treated group (Z). All underwent surgically induced IAs. After surgery, the treatment group received intraperitoneal injections of zinc at three mg/kg/day for four weeks. The vehicle group was administered an equal amount of phosphate-buffered saline. The animals were then sacrificed to measure aneurysm size and wall thickness ratio.

At four weeks, the mean aneurysm size was 37.1  $\mu$ mol in the Z group and 80.4  $\mu$ mol in the V group. The wall thickness ratio was 0.30 in the vehicle group and 0.59 in the zinc group ( $p < 0.01$ ). The V group showed robust accumulation of Iba-1-positive macrophages in the IA walls compared with the Z group demonstrating that zinc supplementation decreased the inflammatory burden in the blood vessel walls.

**Conclusion:** This animal study used surgically induced intracranial aneurysms to demonstrate that the administration of zinc inhibited the growth of experimental IAs and decreased infiltration of inflammatory cells.

Hayashi, K., et al. Association of Zinc Administration with Growth Suppression of Intracranial Aneurysms via Induction of A20. *J Neurosurg.* 2021, March; 134(3): 992-998.

## FISH SKIN GRAFT FOR BURNS

Currently, the gold standard treatment for severe burns is the split-thickness skin graft. These grafts have substantial donor site morbidity and are often not possible when there is no donor skin available. This study compared FDA-approved

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alternatives, from fetal bovine dermis (FBD) to acellular fish skin grafts (FSG) created from minimally processed fish skin from the Atlantic Cod.

This animal study involved anesthetized pigs who received deep, full-thickness burn wounds. The wounds were excised one-day post-burn. The wounds were treated with omega-3 rich acellular FSG or FBD. Digital images and biopsies were performed on days seven, 14, 21, 45 and 60.

Each surgical procedure produced granulated tissue that would be receptive to skin grafts. The FSG group demonstrated granulated tissue one week earlier than did the FBD group. Compared to the FBD treated wounds, those treated with FSG had faster re-epithelialization and greater reduced wound size by day 14 as compared to FBD (50.2% versus 23.5% and 93.1% versus 106.7%, respectively;  $p < 0.005$  for both comparisons).

**Conclusion:** This animal study demonstrates that acellular fish skin grafts may be superior to the more traditional fetal bovine dermis for the treatment of burns.

Stone, R., et al. Accelerated Wound Closure of Deep Partial Thickness Burns with Acellular Fish Skin Graft. *Int J Mol Sci.* 2021; 22(4): 1590.

### **LEMBOREXANT FOR INSOMNIA**

The orexin/hypocretin system plays an important role in regulating the sleep/wake cycle through the promotion of wake drive and arousal. Dual orexin receptor antagonists (DORAs) are thought to facilitate sleep by suppressing the orexin-mediated wake drive. This study reports on the efficacy and safety of lemborexant, a competitive antagonist at both the orexin type I and receptor type II.

This global, multicenter trial included 971 adults with sleep onset and/or sleep maintenance disorders. The eligible adults reported a sleep onset latency (sSOL) of 30 minutes or more and/or subjective wake after sleep onset (sWASO) of 60 minutes or more at least three times a week. Subjects were randomized to receive a placebo, lemborexant, 5 mg, or lemborexant, 10 mg, at bedtime. The primary efficacy endpoint was the subject's estimated time from the attempt to sleep until sleep onset (sSOL). Other parameters included time to wake during the night after sleep onset

(sWASO) and subjective total sleep time (sTST).

At six months, the percent who reported a reduced sSOL by at least 20 minutes included 45.5% of LEM5 and 44.9% of LEM 10 compared with 30.4% of the placebo group. At 12 months, these percentages were similar. In addition, compared with placebo, significant reductions in sWASO were noted for both the LEM5 ( $p < 0.05$ ) and LEM10 ( $p < 0.05$ ) groups. Adverse events leading to withdrawal from the study occurred in 3.8% of the placebo group, 4.1% of the LEM5 group and 8.3% of the LEM10 group.

**Conclusion:** This study of patients with insomnia found that lemborexant, a competitive antagonist at both orexin receptors type I and type II, can improve sleep onset, time awake during the night and subjective total sleep time.

Yardley, J., et al. Long-Term Effectiveness and Safety of Lemborexant in Adults with Insomnia Disorder: Results from a Phase 3, Randomized, Clinical Trial. *Sleep Med.* 2021, April; 80: 333-342.

### **MAGNESIUM FOR MIGRAINES**

Migraine is the second most disabling neurologic condition in the United States. Several studies have found that magnesium is associated with both the function of serotonin and the regulation of vascular tone. This study comparing the relative efficacy of magnesium with that of metoclopramide and prochlorperazine for the treatment of headache and migraine.

The study included adult patients presenting to the emergency department with a chief complaint of migraine headache. Eligible patients were randomized to receive either magnesium sulfate 2 g/50ml D5W, delivered over 20 minutes, metoclopramide 10 mg or prochlorperazine 10mg. The primary outcome variable was the change from baseline on the 11-point Numeric Rating Scale (NRS).

Data were completed for 157 patients. The median change in NRS pain scores at 30 minutes was three for all groups. The median changes in NRS at 60 minutes were four in the magnesium group, three in the metoclopramide group and 4.5 in the prochlorperazine group ( $p = 0.66$ ). A *post hoc* noninferiority analysis revealed that magnesium treatment was non-inferior to the other two.

**Conclusion:** This study of patients with acute migraine

headaches found no significant difference in efficacy between treatment with IV magnesium and that of either metoclopramide or prochlorperazine.

Kandil, M., et al. MAGraïne: Magnesium Compared to Conventional Therapy for Treatment of Migraines. *Am J Emerg Med.* 2021, Jan; 39: 28-33.

### EARLY VERSUS DELAYED OUTCOMES OF ACROMIOCLAVICULAR JOINT RECONSTRUCTION

Previous studies have reported improved outcomes for early, as compared with delayed, reconstruction for high grade acromioclavicular (AC) joint dislocations. However, most are based on older techniques that did not involve reconstruction of both the coracoclavicular (CC) and AC joint ligaments. This study compared functional outcomes of early versus delayed surgical intervention of AC joint dislocations managed with these newer surgical techniques.

This retrospective, comparative study included consecutive patients with AC Rockwood  $\geq$ III injuries (n=54) who underwent stabilization within two weeks (early; n=31) or delayed (n=22) of injury. The primary outcome measure was the Acromioclavicular Joint Instability Scale (ACJIS). Other evaluations included Taft scores, Subjective Shoulder Values (SSV), pain on a Visual Analogue Scale (VAS) and overall satisfaction (zero to 10).

This study found no significant differences between the early and delayed groups for ACJI scores (p=0.267), Taft scores (p=0.084), SSV scores (p=.427), pain on the VAS (p=0.541) or overall patient satisfaction (p=0.491).

**Conclusion:** This study of patients with high grade acromioclavicular joint dislocations found no benefit to early surgical intervention, even using the latest surgical techniques.

Lädermann, A., et al. Early and Delayed Acromioclavicular Joint Reconstruction Provide Equivalent Outcomes. *J Shoulder Elbow Surg.* 2021, March; 30(3): 635-640.

### ANKLE TAPE AND PROPRIOCEPTION

Taping is often recommended as a strategy for preventing ankle

sprains. Improved proprioception has been hypothesized as a plausible reason for such injury prevention. This study examined whether ankle taping changes proprioception acuity immediately after application and whether it is maintained during an athletic event.

Subjects were 53, pre-elite, female netball players with an average age of 17 years. At baseline, proprioceptive acuity was tested using the Active Movement Extent Discrimination Apparatus (AMEDA). Athletes were then randomized to either a self-applied or a physiotherapist-applied tape group. Following ankle taping, the athlete's proprioception was promptly assessed by testers held blind to the taping condition. Immediately after competition in a netball competition, proprioception was assessed before and after tape removal.

Significant improvement in AMEDA scores was observed with either self or physiotherapist-applied tape (p=0.05 and p<0.01, respectively). These improvements were maintained during a netball competition for both conditions. No significant difference in AMEDA scores was noted between the self-applied and the physiotherapist-applied taping conditions (p=0.90).

**Conclusion:** This study demonstrates that proprioception is enhanced by taping of the ankle, with similar effects noted when the tape was self-applied and when applied by a physiotherapist.

Smyth, E., et al. Does Ankle Tape Improve Proprioception Acuity Immediately after Application and Following a Netball Session? A Randomised Controlled Trial. *Phys Ther Sport.* 2021, March; 48: 20-25.

### WUQINXI EXERCISE FOR KNEE OSTEOARTHRITIS

For patients with knee osteoarthritis (KOA) exercise therapy is among the primary recommendations for long-term musculoskeletal pain management. Wuqinxi Qigong (WQX) is a traditional Chinese health technique introduced around 200 AD. This study compared the effects of WQX with those of a traditional resistance and aerobic exercises.

Subjects were 68 patients with KOA, 60 to 90 years of age, randomly allocated to an experimental or control group. The WQX program included exercise for 40 to 45 minutes and five minutes of cool down. The control group (CG)

exercised for a similar time per day, four times per week, with resistance training and aerobic training at 75 to 85% of their heart rate maximum.

Baseline and follow-up tests included the Berg Balance Scale (BBS), the Timed Up and Go Test (TUG), the Six-Min Walk Test (6MWT) and the 30-s Chair Stand Test (30sCST). Knee pain and physical function were assessed with the function subscore of the Western Ontario and McMaster Universities Osteoarthritis Index questionnaire score (WOMAC).

The WQX group improved significantly from pre-test to follow-up on six measures: WOMAC pain, 30sCST, TUG, BBS, isokinetic knee flexion, and extension strength (all p <0.05). In contrast, the CG significantly improved only in 6MWT (p<0.01). The VAS pain scores improved from 7.2 to 6.5 in the CG group (p=0.75) and 7.8 to 5.3 in the WQX group (p=0.027).

**Conclusion:** This study of patients 60 to 90 years of age found that Wuqinxi Qigong may be an effective home exercise program for improving pain and function.

Xiao, C., et al. Follow-up of a Wuqinxi Exercise at Home Programme to Reduce Pain and Improve Function for Knee Osteoarthritis in Older People: A Randomized, Controlled Trial. *Age Ageing.* 2021, March; 50 (2): 570-575.

### RISK OF REVISION AFTER HIP ARTHROPLASTY

Over the past several decades, many joint registries have been created to collect data and provide a national perspective on outcomes and performance of total hip arthroplasty (THA). This study investigated the lifetime risk of revision of THA, using one such registry.

Data for this study were obtained from the New Zealand Joint Registry (NZJR) which recorded all THA procedures since 1999 for patients who were over age 45 years at the time of surgery. Data from the New Zealand registry of births, deaths and marriages was used to obtain an accurate account of deaths. Pre-surgical medical comorbidities were assessed with the American Society of Anesthesiologists (ASA) rating.

Data were completed for 112,254 primary THA procedures. The 10-year revision-free survival rate for the entire cohort was 93.6%. The risk of revision decreased as the age of THA increased from 27.5% at 45 years of

age to 1.1% at 95 years of age. In addition, a higher ASA rating was associated with a worse result across all age groups. The most common causes for revision were aseptic loosening, infection, periprosthetic fracture and dislocation.

**Conclusion:** This Australian study found that, after a total hip arthroplasty, the lifetime risk of revision was greater among younger patients, reaching almost 28% for those ages 46 to 55 at the time of surgery.

Nugent, M., et al. The Lifetime Risk of Revision following Total Hip Arthroplasty. *Bone Joint J.* 2021; 103-B(3): 479-485.

### INTENSIVE ACUPUNCTURE FOR KNEE OSTEOARTHRITIS

Treatment options are limited for patients with osteoarthritis of the knee (KOA). While several studies have been published demonstrating the efficacy of acupuncture for symptoms of KOA, little is known about the effects of electroacupuncture. This study evaluated the effects of electroacupuncture (EA) for the treatment of KOA.

This multicenter, randomized, controlled trial recruited patients 45 to 75 years of age with radiographically confirmed KOA of at least six months' duration. The subjects were randomized to one of three groups to receive 30-minute sessions three times per week for eight weeks. The groups included a sham acupuncture (SA) group, a manual acupuncture (MA) group, that received no electrical current and an EA group that received treatment including an electrical current of 2/100 Hz. The primary outcome measure was the "response rate", defined as the proportion of participants who simultaneously achieved minimal clinically important improvement in pain and function by week eight. Function was assessed using the Western Ontario and McMaster University's Osteoarthritis Index function subscale, while pain was assessed using the Numerical Rating Scale (NRS).

Data were completed for 442 patients. At week eight, response rates were 60.3% in the EA group, 58.6% in the MA group and 47.3% in the SA group, (EA versus SA;  $p=0.0507$ , and MA versus SA  $p=0.023$ ). The response rates in the EA and MA groups were both significantly higher than those in the SA group at weeks 16 and 26.

**Conclusion:** This study of patients with osteoarthritis of the knee found that acupuncture may be effective in decreasing pain and increasing function, and that electroacupuncture may produce effects more quickly.

Tu, J., et al. Efficacy of Intensive Acupuncture versus Sham Acupuncture in Knee Osteoarthritis: A Randomized, Controlled Trial. *Arthritis Rheum.* 2021, March; 73(3): 448-458.

### OSTEOARTHRITIS AND STROKE INCIDENCE

In recent years, several studies have suggested a potential association between osteoarthritis (OA) and stroke. This study used data from general practices in the United Kingdom to further investigate the relationship between OA and both stroke and transient ischemic attack (TIA).

Subjects were 18 years of age or older without a history of cerebrovascular disease or TIA prior to the index date. Participants without OA were matched to those with OA using propensity scores based on gender, age, index year and vascular risk factors. The cohort was followed for 10 years, comparing the incidence of stroke and TIA between the two groups.

Studies included 160,068 patients with OA and 160,068 patients without OA. The 10-year rates of stroke were 4.5% in the OA group and three percent in the non-OA group ( $p<0.001$ ). A TIA occurred in 3.3% of those with OA and two percent of those without OA ( $p<0.001$ ). A regression analysis determined that OA was positively associated with both stroke (HR 1.45) and TIA (HR 1.55).

**Conclusion:** This large, British cohort study found that osteoarthritis is significantly associated with the incidence of stroke and transient ischemic attack.

Jacob, L., et al. Osteoarthritis and Incidence of Stroke and Transient Ischemic Attack in 320,136 Adults Followed in General Practices in the United Kingdom. *Joint Bone Spine* 2021, March;88(2):105104.

### BODY WEIGHT CHANGES DURING THE PANDEMIC

During the COVID-19 pandemic, most governments issued shelter in place orders. This study investigated

the body weight changes associated with this social isolation.

Data were obtained from February 1 to June 1, 2020, using data from the Health Heart Study. All eligible participants reported weight measurements from Bluetooth-connected Smart Scales. Weight change before and after the onset of shelter in place directives was studied.

From 269 participants, 7,444 weight measurements were obtained. After shelter in place orders were initiated, participants experienced steady weight gain at a rate of 0.27 kg every 10 days. This finding was irrespective of geographic location or comorbidities and resulted in a weight gain averaging 1.5 pounds per month.

**Conclusion:** This study found that shelter in place orders have resulted in significant weight gains, suggesting unintended health consequences from this social isolation.

Lin, A., et al. Body Weight Changes During Pandemic-Related Shelter in Place in a Longitudinal Cohort Study. *JAMA.* 2021; 4(3): e212536.

### SAFFRON FOR MOOD AND RESPONSE TO STRESSORS

Saffron, produced from the dried stigma of *Crocus Sativus L.*, is used in traditional Asian medicine for a range of physical disorders. Recent studies have suggested that saffron may be effective as an antidepressant. This randomized, placebo-controlled, double-blind, parallel-group study assessed the acute and chronic effects of saffron for adults with self-reported anxiety, stress, or depression.

Subjects were 73 adults, 18 to 60 years of age, who self-reported feelings of anxiety and/or stress and low mood in their daily lives. The participants were randomly assigned to receive 30 mg of saffron extract or a placebo twice per day. Acute responses to a lab-based psychosocial stressor, the Observed Multitasking Stressor (OMS), were measured through psychological and physiological parameters. The primary outcome measure was the POMS Total Mood Disturbance (TMD) score. Subjective anxiety, stress and depressive feelings were assessed using a questionnaire battery including the Profile of Mood State-2 (POMS). Physiologic measures of stress were made including changes in urinary crocetin (an antagonist of the non-selective

serotonin receptor agonist mCPP) and heart rate variability.

Compared with the placebo group, the treatment group improved more on the POMS Depression subscale ( $p=0.05$ ), social relationship scores ( $p = 0.007$ ) and positive reinterpretation coping ( $p = 0.010$ ) and demonstrated better levels of urinary crocetin ( $p=0.008$ ) as well as heart rate variability. All experienced an increase in subjective anxiety in response to the POMS protocol.

**Conclusion:** This study found that saffron reduces depressive mood in adults with subclinical mood disturbance, improves appetite and protects against psychosocial stress.

Jackson, P., et al. Effects of Saffron Extract Supplementation on Mood, Well-Being, and Response to a Psychosocial Stressor in Healthy Adults: A Randomized, Double-Blind, Parallel-Group, Clinical Trial. **Front Nutrition.** 2021, February; (7): 606124.

### CHOLESTEROL PROFILES AND COGNITIVE DECLINE

While vascular risk factors can directly increase susceptibility to Alzheimer's disease (AD), a direct association between cholesterol levels and progressive dementia has been inconclusive. This prospective study was designed to better understand this association.

At baseline, residents 60 years of age or older were recruited from among participants in the Shanghai Aging Study. All underwent a physical examination, including a fasting lipid profile and APOE genotyping. Medical history was documented, including vascular risk factors (VRFs). Cognition was evaluated through eight tests, with an expert panel then determining diagnoses related to cognitive function, including dementia, for each participant. At follow-up, the association between baseline data and progression to dementia was determined. Vascular risk factors were defined as obesity, a history of hypertension, diabetes, stroke, and coronary artery disease.

Subjects were 1,556 adults without baseline dementia, followed for a mean of 5.2 years. Among those with no vascular risk factors, total cholesterol (TC) and lipoprotein cholesterol (LDL-C) were inversely associated with incident dementia. In addition, LDL-C was inversely associated with incident AD. A correlation was found between incremental total cholesterol, LDL-C, and a slower decline in Mini-Mental

State Examination scores. Among participants without VRFs, every 1 mmol/L increase of TC was associated with a 38% decreased risk of all-type dementia (HR, 0.62), and every 1 mmol/L increase of LDL-C was associated with a 53% decreased risk of dementia (HR, 0.47).

**Conclusion:** This Chinese study found that, among patients without a history of hypertension, diabetes, stroke or coronary artery disease, an increase in total cholesterol and lipoprotein cholesterol is associated with a decreased risk of dementia.

Ding D., et al. Cholesterol Profiles and Incident Cognitive Decline among Older Adults: The Shanghai Aging Study. **Age Ageing.** 2021, February 26;50(2): 472-479.

### LIMBIC PREDOMINANT AMNESTIC MILD COGNITIVE IMPAIRMENT

The progression from mild cognitive impairment (MCI) to Alzheimer's disease (AD) has been related to several biomarker characteristics. This study was designed to define the role of in vivo biomarkers of neurodegeneration and pathology, as assessed by [18F]FDG-PET and cerebral spinal fluid (CSF).

Data were retrospectively obtained from databases collected on patients with MCI or AD who had baseline measures of CSF and an [18F]FDG-PET scan. Included in the present study were only those subjects showing the limbic-predominant pattern (LPP  $n=40$ ) or the AD-like pattern ( $n=20$ ) of MCI. CSF was analyzed for A $\beta$ 42, t-tau and p-tau levels. Each [18F]FDG-PET single-subject scan tested for brain "hypometabolism", as judged by a panel of clinicians held blind to the condition. The Mini-Mental State Examination (MMSE) and Clinical Dementia Rating scale (CDR) global score were used to evaluate global cognitive status.

At follow-up, those in the LPP group showed clinical stability over a mean 8.2-year follow-up, with no decline in MMSE scores, and only seven percent conversion to dementia. Those in the AD group had a high rate of progression to dementia (86%) over a shorter follow-up period (6.47 years). With no differences at baseline, follow-up scores were significantly worse in the AD-like than in the LPP group for MMSE scores ( $p<0.001$ ), Functional Activities Questionnaire scores ( $p<0.01$ ) and Cognitive Dementia Rating Scale global scores ( $p<0.001$ ).

**Conclusion:** This study of patients with an amnesic presentation of mild cognitive impairment found that individuals with the limbic predominant hypometabolism pattern were very unlikely to progress to Alzheimer's disease.

Tondo, G., et al. Biomarker Based Stability in Limbic-Predominant Amnesic Mild Cognitive Impairment. **Eur J Neurol.** 2021, April. 28(4): 1123-1133.

### ERENUMAB FOR HIGH-FREQUENCY MIGRAINE

Erenumab is an FDA-approved, fully human Ig-2 monoclonal antibody that blocks the calcitonin gene-related peptide receptor, for migraine prevention. This large multicenter prospecting cohort real-life trial investigated the effect on migraine symptoms during the first three months of treatment.

The erenumab in Real Life in Italy (EARLY) study included 372 patients 18-65 years of age with chronic high-frequency episodic migraine (HFEM) or chronic migraine (CM). Each patient was treated with one dose of erenumab 70 mg subcutaneously every four weeks. Patients recorded their symptoms in a headache diary, including a rating of their pain using a visual analog scale (VAS) and migraine disability using the Headache Impact Test (HIT-6).

Erenumab was effective for both patient groups (HFEM and CM) at four, eight and twelve weeks in decreasing monthly migraine days (MMDs), median monthly analgesic intake and VAS scores. At nine to 12 weeks, treatment with erenumab decreased MMDs by 4.5 days for those with HFEM, and by 9.3 days for those with CM. VAS pain scores followed a similar pattern, reduced by 1.7 in the HFEM group and 1.9 in the CM group. At week 12, a  $\geq 50\%$  reduction in pain was found among 59.4% of the HFEM group and 55.5% of the CM group.

**Conclusion:** This study of patients with chronic and high-frequency episodic migraines found that erenumab, a monoclonal antibody, may reduce pain and analgesic medication use.

Barbanti, P., et al. Erenumab in the Prevention of High-Frequency Episodic and Chronic Migraine: Erenumab in Real Life in Italy (Early), the First Italian Multicenter, Prospective, Real-Life

### MENISCAL SYMPTOMS AND CARTILAGE DAMAGE

Patients who experience mechanical symptoms of the knee such as locking or catching have often been addressed as having meniscal pathology. This study evaluated the association between various intra-articular pathology including cartilage and meniscal damage with preoperative patient-reported knee symptoms (PRKS).

Subjects were consecutive patients undergoing arthroscopic knee surgery between August 2012 through December 2019. All were undergoing arthroscopy for the presence of classically defined mechanical and meniscal symptoms as demonstrated by the history, physical, and/or MRI. Intra-articular findings were compared to PRKS, using a symptom score derived from three questions from the Knee injury and osteoarthritis Outcome (KOOS) questionnaire; a) Does your knee catch or hang up when moving? b) Do you feel grinding, hear clicking, or any other type of noise when your knee moves? c) What amount of knee pain have you experienced in the last week during twisting/pivoting on your knee? Cartilage damage was graded using the Outerbridge Grade.

Data were completed for 565 patients, 12-81 years of age. The mean average symptoms score was 2.1 for those without meniscal tears, 2.1 for those with a stable meniscal tear pattern, and 2.2 for those with an unstable meniscal pattern. The mean symptom score was 2.0 among those with an Outerbridge grade of <3 compared with 2.3 among those with a grade of  $\geq 3$  ( $p < 0.001$ ). The mean average symptom scores also increased with the burden of cartilage damage as defined by the number of compartments involved, from 1.9 for those with no compartment involvement to 2.4 for those with tricompartmental damage ( $p < 0.001$ ).

**Conclusion:** This study of patients undergoing knee arthroscopic surgery found that symptoms traditionally labeled as meniscal were more associated with cartilage damage than meniscal damage.

Farina, E., et al. Meniscal and Mechanical Symptoms are Associated with Cartilage Damage, Not Meniscal Pathology. **J Bone**

### TRANSTHYRETIN AND RISK OF HEART FAILURE

Transthyretin is one of several proteins that can cause amyloidosis. Transthyretin amyloidosis with cardiac involvement is the most common phenotype of transthyretin amyloidosis. However, the prevalence of transthyretin cardiac amyloidosis is uncertain in the general population. This study assessed the association between plasma transthyretin and incident heart failure in the general population.

Data were obtained from 16,967 participants with consecutively ascertained plasma transthyretin levels from two prospective studies of the Danish population, including the Copenhagen General Population Study (CGPS) and the Copenhagen City Heart Study (CCHS). Information on the diagnosis of heart failure was obtained from the Danish National Patient Registry which records all patient contacts with all clinical hospital departments of outpatient clinics and Denmark. The association between transthyretin levels and heart failure was compared.

In a multivariable adjusted analysis, compared with individuals with transthyretin between the fifth and 95th percentile, those with concentrations below the 5th percentile had a higher risk of HF, calculated as 60% higher in the CGPS and 40% in the CCHS cohorts. The risk for HF was also increased in genetic variants of the TTR genotype.

**Conclusion:** This study found that low plasma transthyretin levels are associated with a higher risk of incident heart failure.

Greve, A., et al. Association of Low Plasma Transthyretin Concentration with Risk of Heart Failure in the General Population. **JAMA Cardiology.** 2021,6(3): 258–266.

### TRANSCRANIAL MAGNETIC STIMULATION FOR CONCUSSION

While most people who sustain a mild traumatic brain injury (mTBI) recover within three months, 15 to -20% experience persistent post-concussive symptoms (PPCS). As previous studies have demonstrated that repetitive transcranial magnetic stimulation (rTMS) may positively impact the symptoms of patients with TBI, this study explored the safety

and efficacy of an accelerated rTMS protocol for patients with mTBI.

Subjects were 15 adults with PPCS due to an injury sustained within the previous five years. All were evaluated with tests of cognition and affect. Each subject underwent twice-daily sessions of rTMS with low frequency (1 Hz) stimulation over the right dorsolateral prefrontal cortex at 110% of the resting motor threshold (rMT). Weekday, twice daily treatment was applied, allowing for a total of 30 treatment sessions over the course of three weeks. Baseline and follow-up testing results were compared. The primary outcome measure was the Post-Concussion Symptom Scale (PCSS).

The mean PCSS score at baseline was 72.5, falling to 48.4 at follow-up ( $p=0.002$ ). Significant gains were also noted on the Beck Depression Inventory ( $p=0.001$ ) and the Beck Anxiety Inventory ( $p=0.000$ ). Among cognitive tasks, significant gains were made on the Trail Making Test, Forms A ( $p=0.002$ ) and B ( $p=0.001$ ), as well as in category fluency ( $p=0.02$ ), phonemic fluency ( $p=0.005$ ) and the Digit Span subtest - forward section ( $p=0.007$ ). All subjects reported headaches, although none reported one with a severity sufficient to discontinue the trial.

**Conclusion:** This study of adults with persistent post-concussive symptoms found twice-daily repetitive transcranial magnetic stimulation to be effective for improving cognition and affective symptoms.

Meek, B., et al., Accelerated Repetitive Transcranial Magnetic Stimulation in the Treatment of Post-Concussion Symptoms Due to Mild Traumatic Brain Injury: A Pilot Study. **Brain Inj.** 2021, 35; 1, 48-58.

### LONG-TERM OUTCOME OF NONOPERATIVE TREATMENT OF ACROMIOCLAVICULAR INJURY

Acromioclavicular (AC) injuries are classified according to the Rockwood classification in which Rockwood I (R1) and II(RII) are incomplete dislocations. These are usually treated with short-term shoulder immobilization and nonsteroidal anti-inflammatory drugs. This study assessed the long-term outcomes of non-operative intervention for R1 and RII injuries.

Eligible subjects were 16 years of age or older presenting to the author's emergency room with a diagnosis of AC dislocation, either R1 or RII. Baseline data included gender,

age, dominant side, laterality of injury and body mass index. The primary measures were the Constant score, the Disabilities of the Arm Scale, the Shoulder and Hand questionnaire (DASH) 12, and the Simple Shoulder Test (SST).

During the 12 years of the study, 2,075 patients were seen for RI and RII injuries. At a median of 85 months, the mean Constant score of the injured shoulder was 88.6 and that of the uninjured shoulder was 93.3. The differences between shoulders for the adjusted Constant scores were significant for both RI and RII injuries. The median patient satisfaction for RII injuries was 85, while that for RI injuries was 80. A radiographic comparison of the injured and contralateral shoulder found that patients had similar rates of degeneration (44% vs 46%) but more frequent osteolysis of the distal clavicle (31% vs 0%), ossification of the ligaments (29% vs 7%), and deformity of the distal clavicle (19% vs 0%), significant ( $p < 0.001$ ) for all comparisons.

**Conclusion:** This study of patients with acromioclavicular injuries, Rockwood I and II, found that, after conservative therapy, long-term functional outcome of the injured shoulder was inferior to the contralateral shoulder.

Verstift D., et al. Long-term Outcome after Nonoperative Treatment for Rockwood I and II Acromioclavicular Joint Injuries. *Am J Sports Med.* 2021, March; 49(3): 757-763.

### UNMET ADAPTIVE EQUIPMENT NEEDS

For adults who are faced with age-related health and mobility decline, remaining at home often requires adaptations and equipment to reduce the risk of adverse events. This study was designed to determine how many older adults in the US need adaptive equipment and how many individuals have unmet needs.

This observational cohort study used secondary data from the National Health and Aging Trends Study (NHATS) from May 2015 to October 2019. The NHATS uses a representative sampling of US citizens. For this study, subjects were chosen who were community-dwelling, and 65 years of age or older. To determine the need for such equipment, researchers developed deficit-based criteria, selecting people based on diminished capability for whom most clinicians believe equipment would

unquestionably improve quality of life. Those with bathing and toileting equipment needs in 2015 were followed to determine how many did not receive such equipment. At follow up participants were asked, "Whether or not you use it, does your bathroom have (1) a grab bar in the shower or tub area, (2) a seat for the shower or tub, (3) a raised toilet or raised toilet seat, or (4) grab bars around the toilet?" The percent with unmet needs at follow-up was recorded.

In 2015, 2614 participants met the criteria for needing bathing or toileting equipment. These 2614 individuals (representing 12 million community-dwelling Medicare beneficiaries) were identified as having deficits that would benefit from equipment. Among those in need of bathing equipment, 26% had none, 33% had either a grab bar or a shower seat, and 40% had both. Among those needing toileting equipment, 44% had none, 32% had either a grab bar or a raised toilet seat, and 24% had both. In total, five million individuals in the US had unmet needs for adaptive equipment. After four years of follow-up, 35% of those needing bathing equipment, and 52% of those needing toileting equipment never received such equipment.

**Conclusion:** This nationally representative study of United States citizens found that 42% of adults with impairments that require bathing or toileting equipment do not have that equipment, suggesting a missed opportunity for five million citizens.

Lam, K., et al. Unmet Need for Equipment to Help with Bathing and Toileting Among Older US Adults. *JAMA Intern Med.* Published online March 22, 2021. doi:10.1001/jamainternmed.2021.0204.

### METFORMIN DURING ANTIRETROVIRAL THERAPY

Antiretroviral therapies (ARTs) efficiently control HIV-1 replication and improve the health of people living with HIV (PLWH). However, viral reservoirs persist in cellular/anatomic sanctuaries with viral rebound occurring rapidly with ART interruption. The persistence of these reservoirs is associated with chronic inflammation/immune activation, alterations of the intestinal mucosal homeostasis and metabolic disorders. Within the intestine, rapamycin (mTOR) is important for gastrointestinal participation in this storage process. As metformin impedes mTOR activation/phosphorylation, the authors

evaluated the immunological and virological effects of metformin supplementation during ART.

Subjects were non-diabetic individuals with PLWH, presenting with relatively low CD4/CD8 ratios ( $< 0.8$ ). The subjects were given metformin, 500 mg bid, titrating up to 850 mg twice per day. Blood was taken at baseline, after 12 weeks of metformin treatment (Week 12), and 12 weeks after metformin discontinuation. Blood samples were analyzed to determine CD4+ T-cell counts, CD4+/CD8+ T-cell ratios, plasma markers of inflammation/gut damage and levels of cell-associated integrated HIV-DNA and HIV-RNA and transcriptionally-inducible HIV reservoirs.

Metformin significantly decreased CD4+ T-cell infiltration in the colon. In addition, metformin significantly reduced mTOR activation/phosphorylation. Further, metformin decreased the HIV-RNA/HIV-DNA ratios, a surrogate marker of viral transcription, in colon-infiltrating CD4+ T-cells of 8/13 participants.

**Conclusion:** This study of people living with HIV found that treatment with metformin decreased intestinal infiltration of memory CD4+ T-cells, and viral transcription, through its effect on rapamycin.

Planas, D., et al. LILAC pilot study: Effects of Metformin on mTOR Activation and HIV Reservoir Persistence during Antiretroviral Therapy. *Eboimed.* 2021, March; 103270.

### BILATERAL ULTRASOUND PALLIDOTHALAMIC TRACTOTOMY FOR PARKINSON'S DISEASE

Bilateral stereotactic neurosurgery for Parkinson's disease (PD) dates back to the late 1940s. Refinements in the technique have been suggested, including the use of focal ultrasound to target the pallidothalamic tract just below the thalamus, with a procedure named "pallidothalamic tractotomy" (PTT). This study assessed the efficacy of MR-guided focused ultrasound (MRgFUS) to apply bilateral PTT.

This pilot trial included 10 patients with mixed and tremor-dominant idiopathic PD with insufficient response to L-dopa. For each patient a standardized bilateral PTT was completed, with sonications for each target lesion sub-unit to provide a thermal dose of at least 240 cumulative equivalent minutes (CEM). For patients who received

(Continued from page 2)

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unilateral PTT prior to 2017, repeat treatment of the first PTT to increase the lesion size was performed for the second side. The primary endpoints included Unified Parkinson's Disease Rating Scale (UPDRS) scores, the on and off medications state, dyskinesias, sleep disturbances, pain, reduction in drug intake, and patient self-assessment.

At one year follow-up, total UPDRS scores, off medication, improved by 52% as compared to baseline on-medication ( $p < 0.007$ ). Comparing the one year off- with baseline on-medication examinations, tremor scores were reduced by 91% ( $p = 0.006$ ), distal rigidity scores were reduced by 67% ( $p = 0.006$ ), and distal hypobradycinesia scores were reduced by 54% ( $p = 0.01$ ). There was an 89% reduction in pain.

**Conclusion:** This study of patients with L-dopa resistant Parkinson's disease found that bilateral pallidothalamic tractotomy could improve pain, tremor, distal rigidity, distal hypobradycinesia, dyskinesias, and dystonia.

Gallay, M., et al. Bilateral MR-Guided Focused Ultrasound Pallidothalamic Tractotomy For Parkinson's Disease With 1-Year Follow-Up. **Front Neurol**.2021. doi.org/10.3389/fneur.2021.601153.

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