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CEREBROLYSIN AND STROKE RECOVERY

Ischemic stroke is the second most common cause of death worldwide, and the third leading cause of loss of disability-adjusted life years. Cerebrolysin, a neuropeptide preparation consisting of low molecular weight neuropeptides and free amino acids, has been shown by animal studies to have neuroprotective properties. This study analyzed the efficacy and safety of cerebrolysin during post-stroke recovery.

Adult patients with ischemic supratentorial strokes were recruited for randomization. The subjects received either cerebrolysin, at 30 mL per day, or a placebo, once daily for 21 days, beginning at one to three days after stroke onset. The primary efficacy criterion was the change in the Action Research Arm Test (ARAT) of upper limb motor function from baseline to day 90. Secondary outcome measures were changes from baseline in gait velocity, fine motor function, global neurologic state, level of disability or dependence in activities of daily living, aphasia, neglect, quality of life and depression.

For the 205 patients included in the study, the ARAT scores improved from 10.1 at baseline to 40.7 on day 90 in the cerebrolysin group, and from 10.7 to 26.5 in the placebo group ($p < 0.0001$). A multivariate assessment of global status, as assessed by 12 outcome measures, demonstrated superiority of the treatment group as compared to the placebo group ($p < 0.0001$).

Conclusion: This study of patients with ischemic stroke found that treatment with cerebrolysin, beginning 24 to 72 hours after stroke onset, had a beneficial effect on functional and global outcome.

Muresanu, D., et al Cerebrolysin and Recovery after Stroke (CARS):

Randomized, Placebo Controlled, Double-Blind, Multicenter Trial. **Stroke.** 2016, January; 47(1): 151-159.

RISING MORBIDITY AND MORTALITY AMONG MIDDLE-AGED, WHITE AMERICANS

There has been a long-term decline in the mortality rate in the United States (US), with rates between 1970 and 2013 reduced for those ages 45 to 54 years by 44%, and with parallel declines in other wealthy countries. This paper reviewed the changes in morbidity and mortality among middle-aged white males in the US after 1998.

Mortality rates for patients 45 to 54 years of age were compared between the United States and six, rich, industrialized countries, including France, Germany, the United Kingdom, Canada, Australia and Sweden. From 1979 to 1998, mortality for US whites fell by two percent on average, which matched the rate of decline in the six comparison countries. After 1998, the other countries continue to average a two percent decline in mortality per year, while the mortality for US whites rose by a half percent per year.

Among the causes of death that accounted for the mortality reversal were suicide, drug and alcohol poisoning and chronic liver disease and cirrhosis. The turnaround in mortality for this age group was primarily driven by increased rates among those with a high school degree or less, with mortality in that group increasing by 134 per 100,000 between 1999 and 2013. Those with a college education of less than a B.A. had little change in mortality, while those with greater amounts of education experienced a decrease in mortality rate of 57 per 100,000.

Conclusion: This population study found that, in the United States, an increase in midlife morbidity and mortality is uniquely occurring among white non-Hispanics, primarily resulting from increases in suicides, drug and alcohol poisoning and chronic liver disease, primarily among the less educated.

Case, A., et al. **Proc Natl Acad Sci USA.** 2015, December 8; 112(49): 15076-15085.

TREATMENT FOR OLECRANON BURSTITIS

Olecranon bursitis is characterized by fluid accumulation in the bursa, occurring with and without inflammation. Treatment options for nonseptic olecranon bursitis include compression bandaging with nonsteroidal anti-inflammatory drugs, aspiration with or without steroid injections or surgical management. This study was designed to determine whether compression bandaging with nonsteroidal anti-inflammatory drugs, aspiration or aspiration with steroid injection is most effective for the treatment of this disorder.

This prospective study included 90 patients, randomized to one of three treatment groups, compression bandaging with nonsteroidal anti-inflammatory drugs (C), aspiration (A) or aspiration with steroid injection (S). The mean symptom duration was four weeks prior to intervention, and the mean follow-up was 12 weeks. Those in the NSAID group received aceclofenac, 100 mg twice per day, while those in the injection group received one mL of 40 mg per mL triamcinolone acetonide. The participants were followed weekly for four weeks.

Group S had the earliest resolution (2.3 weeks) when compared with Group A (3.1 weeks) and Group C (3.2 weeks), $p = 0.015$. However, no significant differences

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were noted between groups at four weeks ($p=0.073$). No complications of treatment were noted for any of the groups.

Conclusion: This study of patients with nonseptic olecranon bursitis found that symptom resolution occurred most rapidly in the group treated with aspiration and steroid injection, though no significant difference in outcomes was noted between groups at four week follow-up.

Kim, J., et al. A Randomized Trial among Compression Plus Nonsteroidal Anti-Inflammatory Drugs, Aspiration, and Aspiration with Steroid Injection for Nonseptic Olecranon Bursitis. *Clin Ortho Rel Res.* 2016, March; 474(3): 776-783.

METABOLIC SYNDROME AMONG MARIJUANA USERS

In 2013, 19.1% of emerging adults, ages 18 to 25, reported current marijuana use. As the metabolic syndrome is a known risk factor for type II diabetes and cardiovascular disease, this study evaluated the relationship between marijuana use and the metabolic syndrome.

Data were obtained from the National Health and Nutrition Examination Survey (NHANES), with marijuana use determined through a questionnaire. Among those who used marijuana, frequency of use was characterized. The primary outcome measure was the metabolic syndrome, including at least three of the following risk factors: waist circumference, systolic/diastolic blood pressure, HDL cholesterol, triglycerides and fasting glucose. The data were reviewed to examine the relationship between marijuana use and the presence of the metabolic syndrome among emerging adults, adults and middle aged adults.

The data revealed that 13.8% of current and 17.5% of past marijuana users presented with the metabolic syndrome, compared with 19.5% of never users ($p=0.0003$ and $p=0.03$, respectively). Among male, current users, the prevalence of elevated waist circumference was significantly lower than among never users ($p<0.0001$). Among emerging adults, current marijuana users had lower odds of the metabolic syndrome than never users. Among adults, no

significant relationship was found between marijuana use and the metabolic syndrome. Among middle-aged adults, current and former marijuana users had lower odds of presenting with the metabolic syndrome compared to never users.

Conclusion: This study found that current and past marijuana use are both associated with a lower prevalence of the metabolic syndrome.

Vidot, D., et al. Metabolic Syndrome among Marijuana Users in the United States: An Analysis of National Health and Nutrition Examination Survey Data. *Am J Med.* 2016, Feb.; 129(2): 173-179.

SIGNIFICANCE OF LOSS OF CONSCIOUSNESS AT ONSET OF SUBARACHNOID HEMORRHAGE

Subarachnoid hemorrhage (SAH) commonly presents with a loss of consciousness (LOC). This study was designed to further understand the significance of LOC at the onset of SAH.

This retrospective analysis included data from 1,482, consecutively treated patients with SAH. Those admitted to Columbia Presbyterian Hospital within 14 days of hemorrhage were included. LOC was determined by interview with patients, families and first responders. Patient records were assessed for in-hospital mortality, and for outcomes after discharge, including modified Rankin scale (mRS) scores at three and 12 months, as well as hospital complications.

Of the 1,482 patients enrolled in the outcome study, 590 were noted to have LOC at onset of SAH. Compared to those who did not lose consciousness, those with LOC had more cisternal and intraventricular blood on CT scan, as well as global cerebral edema, parenchymal hematoma, hydrocephalus and acute infarction. Patients with LOC were also more likely to have an aneurysm coiled rather than clipped. At 12 months, 51.2% of patients with LOC were dead or severely disabled, as compared with 17.7% of those without LOC ($p<0.001$). LOC was significantly related to functional outcome at 12 months ($p=0.003$).

Conclusion: This study patients with subarachnoid hemorrhage found

that loss of consciousness at onset is a robust indicator of severe bleeding and worse outcome, including death and disability.

Suwatchcharangkoon, S., et al. Loss of Consciousness at Onset of Subarachnoid Hemorrhage as an Important Marker of Early Brain Injury. **JAMA Neurol.** 2016, January; 73(1): 28-35.

RISK OF PRE-STROKE ANTIPLATELET THERAPY

Intravenous tissue plasminogen activator (tPA) is known to improve outcomes after ischemic stroke. Many patients receive antiplatelet therapy before ischemic stroke, with the concern that those individuals might face an increased risk of bleeding when treated with tPA. This study assessed the risks and benefits associated with pre-stroke antiplatelet therapy among patients with ischemic stroke who received intravenous tPA.

Data were obtained from 85,072 adult patients with ischemic stroke who received intravenous tPA. Of these, 38,844 had been receiving antiplatelet therapy before hospital admission. The participants were followed for outcomes including symptomatic intracranial hemorrhage (sICH), in-hospital mortality, discharge ambulatory status and modified Rankin scale score (mRS).

After risk adjustment, the prior use of antiplatelet agents was found to be associated with a higher onset of sICH (OR 1.18), with a small, absolute increased risk of 0.68%. Prior antiplatelet therapy was not associated with a significantly greater risk of in-hospital mortality. Those receiving antiplatelet therapy had higher ratios of being discharged to home, of independent ambulation and of better mRS scores at discharge.

Conclusion: This study of patients with acute ischemic stroke who received tPA found that those receiving pre-stroke antiplatelet therapy were at increased risk of symptomatic intracranial hemorrhage, but also had better functional outcomes than those who had not received antiplatelet therapy.

Xian, Y., et al. Risks and Benefits Associated with Pre-Stroke Antiplatelet Therapy among Patients with Acute Ischemic Stroke Treated with Intravenous Tissue Plasminogen

Activator. **JAMA Neurol.** 2016, January; 73(1): 50-59.

ACTIVE SHOULDER MOTION MEASUREMENT USING AN INFRARED DETECTION SYSTEM

Restoration of active motion of the shoulder is a major treatment goal for patients with shoulder conditions. Variability in clinical measurement of the shoulder motion can make it difficult to evaluate a patients' progress. This study investigated the utility of a widely available infrared system for measuring shoulder motion.

This study used the Microsoft Kinect system, which employs infrared laser light and depth sensing cameras to determine positions of the arm and shoulder. Measurements were made for 10, normal, adult volunteers using the Kinect system, with those results compared with measurements made using standardized, anteroposterior and lateral photographs, taken concurrently. Measurements were made in five different positions of abduction, flexion, rotation and cross body adduction. The relationship between the two measurement methods was determined using linear regression. The results of the ROM measurements as determined by the Kinect system was compared with the ability to perform the Simple Shoulder Test (SST).

For the 10 control subjects, the Pearson correlation coefficients for the different positions were 0.997, 0.992, 0.982 and 0.995. The average time to document the five motions in both shoulders was 4.8 minutes. The Kinect measures of active motion correlated with the patients' self-assessments of their ability to perform the SST, with Pearson correlation coefficients of 0.79 for abduction, 0.67 for flexion, 0.56 for external rotation, 0.5 for internal rotation and 0.33 for cross-body adduction.

Conclusion: This study found that an infrared system without attached markers can provide a quick and accurate measurement of range of motion in the upper limb.

Matsen, F., et al. Measurement of Active Shoulder Motion Using the Kinect, a Commercially Available Infrared Position Detection System. **J**

Shoulder Elbow Surg. 2016, February; 25(2): 216-223.

BLIND CORTICOSTEROID INJECTIONS FOR ADHESIVE CAPSULITIS

While adhesive capsulitis has been described as a self-limiting condition, long-term studies suggest that residual pain may occur in up to 50% of patients. As intra-articular steroid injections have been shown to provide significant short-term benefits for pain relief and increased range of motion, this study assessed the effect of a single intra-articular corticosteroid injection, performed without image guidance, when applied before physical therapy.

This blinded, randomized, controlled trial was performed at a single Argentinian center between June of 2012 and June of 2013. Subjects were adult patients with stage II adhesive capsulitis according to the classification of Hannafin and Chiaia. Eighty-seven consecutive patients with frozen shoulder were randomized to receive either a single corticosteroid injection into the glenohumeral joint or oral diclofenac, 75 mg twice a day. All subjects then engaged in a progressive rehabilitation protocol. Clinical and functional parameters were determined at baseline and at two, four, eight and 12 weeks.

The corticosteroid group had faster pain relief and shoulder function improvement during the first eight weeks ($p < 0.001$). At 12 weeks, no significant difference was seen between the groups. Forward flexion, abduction and internal rotation were significantly improved in the steroid group as compared to the control group at all time points ($p < 0.001$).

Conclusion: This study of adults with adhesive capsulitis found that pain and functional improvement, through physical therapy, could be better accelerated with a blind intraarticular steroid, than with oral NSAIDs.

Ranalletta, M., et al. Corticosteroid Injections Accelerate Pain Relief and Recovery of Function Compared with Oral Nonsteroidal Anti-Inflammatory Drugs in Patients with Adhesive Capsulitis: A Randomized, Controlled Trial. **Am J Sports Med.** 2016, Feb; 44(2): 474-481.

MESENCHYMAL STEM CELLS IN FACET JOINTS AND INTERSPINOUS LIGAMENTS

In degenerative diseases of the spine, the posterior longitudinal ligament and the ligamentum flavum ligament and associated joints can become hypertrophied and ossified. While the etiology of these conditions remains largely unknown, mesenchymal stem cells (MSCs) are believed to play an important role. This study was designed to detect the presence of MSCs in the facet joints and interspinous ligaments of patients with degenerative joint disease of the spine.

Subjects were ten patients scheduled for posterior lumbar decompression surgery. At surgery, facet joints and interspinous ligaments were harvested, with mesenchymal stem cells extracted and cell surface markers analyzed using flow cytometry. The cells were then analyzed *in vitro* after exposure to differentiating agents while in cell culture.

The stem cells derived from the facet joint and interspinous ligaments were found to have a tri-lineage potential to be differentiated into osteogenic, adipogenic and chondrogenic cells, depending upon the induction environment to which they were exposed.

Conclusion: This study of tissue harvested from patients undergoing spine surgery for spinal stenosis isolated stem cells which showed high proliferation rates which could differentiate into osteoblasts, adipocytes, and chondrocytes, depending upon the microenvironment.

Kristjansson, B., et al. Isolation and Characterization of Human Mesenchymal Stem Cells from Facet Joints and Interspinous Ligaments. *Spine*. 2016, January; 41(1): E1-E7.

INCIDENCE OF SPINAL FRACTURE IN ANKYLOSING SPONDYLITIS

Ankylosing spondylitis (AS) is a seronegative spondyloarthropathy that increases the risk of spinal fractures and spinal cord injury. Previous reports have shown that the lower cervical spine is the most common site for fractures among

those with AS. This study was designed to better understand the incidence and type of spinal fractures in the AS population.

Data were obtained from a national inpatient sample of patients with AS and spinal fractures from 2005 to 2011. This retrospective, cohort study characterized spinal fractures by region and spinal cord injury based on ICD-9 codes. Spinal fractures were further classified by treatment group and by incidence of adverse events.

Of the 939 patients hospitalized with a fracture, 498 were cervical, 393 were thoracic, 171 were lumbar, 14 were sacral and 123 were multiple in region. Of these, 6.6% died during hospitalization. A spinal cord injury occurred in 198 of the 939 patients, with two thirds occurring as a result of cervical, and one third as the result of thoracic, fractures. Among the 276 patients experiencing adverse events during hospitalization, urinary tract infection was the most common, and intubation the second most common.

Conclusion: This study of patients with ankylosing spondylitis found that those hospitalized with a vertebral fracture are at high risk for inpatient complications and mortality.

Lukasiewicz, A., et al. Spinal Fracture in Patients with Ankylosing Spondylitis. Cohort Definition, Distribution of Injuries, and Hospital Outcomes. *Spine*. 2016, February; 41(3): 191-196.

PAIN AMONG OFFSPRING OF PATIENTS WITH TOTAL KNEE REPLACEMENT

Among patients with osteoarthritis (OA) of the knee, pain is the most common presenting symptom. While the mechanism of knee pain is not fully understood, some have suggested demographic, structural, genetic and central factors as contributors. This study was designed to determine whether individuals with at least one parent undergoing a total knee replacement (TKR) for severe, primary knee osteoarthritis would have an increased risk of knee pain, as compared to those with no family history of knee OA.

Subjects included 219 patients, ages 26 to 61 years (115 offspring and 104 controls). At two and 10 years into the study, knee pain was

assessed using the Western Ontario and McMaster University's osteoarthritis index (WOMAC), comparing the offspring of those who did, with the offspring of those who did not undergo a TKR.

After adjusting for confounders and structural factors such as knee cartilage defects, bone marrow lesions, effusions, meniscal extrusion and tears, the offspring of those with TKR were found to be at an increased risk of worsening total knee pain (odds ratio 2.16), and at increased risk for the pain according to each subscale of the WOMAC except for knee pain on a flat surface and standing (all comparisons $p < 0.05$) as compared to the offspring of those without TKR.

Conclusion: This study found that offspring of people with a history of total knee replacement are at an increased risk of worsening knee pain over eight years, suggesting a genetic etiology, independent of structural factors.

Pan, F., et al. The Offspring of People with a Total Knee Replacement for Severe Primary Knee Osteoarthritis Have a Higher Risk of Worsening Knee Pain over Eight Years. *Ann Rheum Dis*. 2016, February; 75(2): 368-373.

PREDICTING ANKLE SPRAIN IN AMERICAN FOOTBALL PLAYERS

Lateral ankle sprains (LASs) are the most common acute and recurrent injuries among athletes, representing 23% of all high school athletic injuries. This study assessed whether clinical tests, focusing on potentially modifiable factors might be useful for predicting LAS.

This prospective cohort study investigated 606 American football players, including 365 high school and 241 NCAA Division I athletes. For all participants, body mass index (BMI) was recorded, with preseason testing with the Star Excursion Balance Test and a modified functional movement screen completed by a certified athletic trainer. The players were followed through the following season to identify those experiencing an LAS.

A significant association was found between BMI and the risk of a LAS ($p < 0.001$), with an odds ratio of 1.4 for those with a BMI of greater than 26.69 kg/m². Of the subsets of

the Star Excursion Balance Test, only performance on the anterior subsegment was significantly associated with the risk for LAS ($p=0.001$), with scores of less than 67% demonstrating a 1.62 odds ratio for LAS as compared to those with scores of greater than 67%.

Conclusion: This prospective study of high school and college football players found that body mass index and the Star Excursion Balance Test-Anterior Performance Subscale were significantly associated with the risk of lateral ankle sprain.

Gribble, P., et al. Prediction of Lateral Ankle Sprains in Football Players Based on Clinical Tests and Body Mass Index. *Am J Sports Med.* 2016, February; 44(2): 460-467.

PRESEASON HIP STRENGTH ASSOCIATED WITH ANTERIOR CRUCIATE LIGAMENT INJURIES

The anterior cruciate ligament (ACL) is most commonly ruptured knee ligament in competitive athletics, with 70% of these injuries deemed noncontact in nature. This study assessed whether isometric hip strength is associated with noncontact ACL injuries.

Subjects were 501 athletes enrolled in a prospective case control study. Preseason hip strength was assessed bilaterally with a hand-held dynamometer, measuring hip abductors and external rotators. All athletes were followed for ACL injuries during the season, which were further classified as contact or noncontact.

Among the athletes, 15 noncontact ACL injuries were identified during the following season. Baseline hip external rotation and hip abduction strength were associated with increased risk of noncontact ACL injury ($p=0.001$ for both comparisons). Strength cutoffs for high risk were determined. For hip external rotator strength, a cutoff of <20.3% of body weight corresponded with a 93% sensitivity and a 59% specificity, as well as a positive likelihood ratio of 2.3, and a negative likelihood ratio 0.11, for injury. For hip abductor strength, a clinical cutoff of <35.4% of body weight corresponded with a sensitivity of 87% and a specificity of 65%, with a positive likelihood ratio of 2.5 and a

negative likelihood ratio of 0.21 for injury.

Conclusion: This prospective study found that both hip external rotation strength and hip abduction strength tests (measured preseason) distinguished between athletes who later sustained an ACL injury.

Khayambashi, K., et al. Hip Muscle Strength Predicts Noncontact Anterior Cruciate Ligament Injury in Male and Female Athletes: A Prospective Study. *Am J Sports Med.* 2016, February; 44(2): 355-361.

BARIATRIC SURGERY AND HEALTH IN ADOLESCENCE

Severe obesity affects 4.4 million children and adolescents in the United States. This study explored the effect of these procedures on weight loss, weight related quality of life, micro-nutritional levels and coexisting conditions among adolescents.

This prospective, multicentered study included consecutive adolescents undergoing bariatric procedures between March of 2007 and February of 2012. Included were 242 obese adolescents with a mean body mass index of 53 kg/m², all of whom underwent gastric bypass or sleeve gastrectomy procedures. Change in body weight, coexisting conditions, cardiometabolic risk factors and postoperative complications were evaluated during the three years post-procedure.

At three years, mean body weight had decreased by 27%. Remission of type II diabetes occurred in 95% of the patients, and remission of prediabetes occurred in 76%. Abnormal kidney function remission occurred in 86%, with remission of hypertension in 74%. Dyslipidemia improved in 66% and weight-related quality of life as measured by the Impact of Weight on Quality of Life-Kids improved from 63/100 to 83/100. However, most participants suffered from micronutrient deficiencies and 13% had undergone further intra-abdominal procedures during the follow up period.

Conclusion: This study of adolescents undergoing bariatric surgery found that weight, cardiometabolic health and weight-related quality of life improved in the three years after surgery, although this surgery was associated with

micronutrient deficiencies and additional intra-abdominal procedures.

Inge, T., et al. Weight Loss and Health Status Three Years After Bariatric Surgery in Adolescence. *N Engl J Med.* 2016, January 14; 374(2): 113-123.

OUTCOMES AFTER CHOPART AMPUTATION

The Chopart amputation is often required in diabetic patients with tissue destruction in the midfoot due to gangrene or infection. While this procedure is considered to be an extreme limb salvage technique, the outcome of these patients is not well understood. This study reviewed the outcomes of 83 patients undergoing Chopart amputation.

Subjects were a consecutive series of diabetic patients undergoing Chopart amputation from 2009 to 2011, with 45.8% with gangrene, 37.4% with abscess and 16.9% with osteomyelitis. Urgent surgery was performed for 67.5% of the patients. The primary outcome measure was limb salvage after amputation. All subjects were followed weekly until the ulcer had healed, and monthly thereafter in the absence of recurrence. The average follow-up period was 2.8 years.

Of the 83 patients, 34 had been referred after failure of a minor foot amputation, with 63 undergoing emergency surgery. At follow-up, 56.6% healed completely at a mean interval of 164.7 days, 13 patients died without having obtained a complete cure and 27.7% underwent major amputation at a mean of 96 days, with an incidence rate of 12.9%. The mean interval to ulcer recurrence in 15 of the patients was 86.3 days. Of the 83 patients, 38 died, with a rate of 45.8% and an incidence rate of 25.8% per year.

Conclusion: This study of 83 consecutive patients undergoing Chopart amputation found that 47% healed at an average of 164.7 days, with major amputation necessary at an annual incidence of 12.9%, and annual incidence of death of 25.8%.

Faglia, E., et al. Outcomes of Chopart Amputation in a Tertiary Referral Diabetic Foot Clinic: Data from a Consecutive Series of 83 Hospitalized Patients. *J Foot Ankle*

HEALTHY MIND, HEALTHY MOBILITY FOR OLDER ADULTS

The incidence of cognitive impairment that does not meet the diagnostic criteria for dementia (CIND) is currently two-fold greater than the incidence of Alzheimer's disease and related dementia. Numerous studies have demonstrated that those who are more physically active are less likely to experience cognitive decline and dementia later in life. This study examined the effect of combining a group-based exercise program with dual-task training on cognitive function in active older adults with indications of CIND.

Subjects were included from an exercise class at the Canadian Centre for Activity and Aging (CCAA), ranging from 55 to 90 years of age. All were free of dementia or other neurologic or psychiatric disorders. Over the 26 weeks of the study, the participants were engaged in a group based exercise program, two to three times per week, plus a weekly square stepping exercise (a visuospatial working memory task that requires a stepping response). The intervention group was required to respond to cognitively challenging questions during the square stepping exercise. The primary outcome measure was the change in global cognitive function (GCF), based upon a cumulative score from a neuropsychological battery.

At 26 weeks, greater improvement was seen in standardized GCF in the treatment group than in the control group ($p=0.04$). At week 26, the treatment group's standardized verbal learning and memory scores were 0.3 standard deviations, and their verbal fluency scores 0.62 standard deviations higher, than those of the control group.

Conclusion: This study of elderly individuals found that a 26 week program of group based exercise, combined with dual task training, improved cognitive function better than did group based exercise alone.

Gill, D., et al. Healthy Mind, Healthy Mobility Trial: A Novel Exercise Program for Older Adults. **Med Sci Sports Exer.** 2016, February; 48(2): 297-306.

MCEMP1 GENE EXPRESSION AND STROKE PROGNOSIS

Stroke is the second leading cause of death worldwide, and remains a major cause of disability among survivors. As genomic technology has progressed, this study evaluated the efficacy of a novel RNA biomarker as an indicator of stroke prognosis.

Subjects were obtained from the INTERSTROKE study, a large international, standardized, case control study of patients from 22 countries. The subjects were 129 patients with blood sampling within five days of symptom onset, and 170 control participants with no history of stroke. From these, total RNA was isolated to identify RNA transcripts associated with stroke.

From the analysis, the most significant gene associated with stroke was found to be MCEMP1, which had a 2.4 fold increased expression in stroke cases, as compared to controls. This gene was tested for associations with known stroke risk factors, with no associations found. MCEMP1 was highest in samples collected within 24 hours of symptom onset, as compared with controls or stroke cases collected after 24 hours. MCEMP1 was increased by 4.5 fold in ICH cases as compared with controls, and by 2.1 in ischemic cases compared with controls.

Individuals with disabilities at one month had a more elevated baseline MCEMP1 than did controls or individuals without disabilities. MCEMP1 expression was independently associated with the one month modified Rankin Score and death.

Conclusion: This study found that the gene expression of MCEMP1 was elevated in patients with stroke, and was associated with increased morbidity and mortality at one month.

Raman, K., et al. Peripheral Blood MCEMP1 Expression Is a Biomarker for Stroke Prognosis. **Stroke.** 2016, March; 47(3): 652-658.

VITAMIN D AND CLINICALLY ISOLATED SYNDROME

Previous studies have demonstrated that levels of 25-hydroxyvitamin D are associated with inflammatory activity among patients with multiple sclerosis (MS). As the

loss of gray matter volume predicts long-term disability among patients with MS, this study was designed to determine any association between 25-hydroxyvitamin D levels among patients with clinically isolated syndrome (CIS) and imaging measures of neurodegeneration.

Data were obtained from subjects in the STAYCIS trial, a randomized study of atorvastatin in patients with recent CIS, used to assess the association of 25-hydroxyvitamin D levels with imaging measures thought to reflect neurodegeneration. All subjects were evaluated clinically and by brain MRI at baseline and at months three, six, nine, and 12. The primary endpoint was the development of at least one MS relapse or at least three new T2 lesions on brain MRI at month 12. The data were reviewed for the relationship between 25-hydroxyvitamin D levels and clinical and MRI measures of inflammatory activity.

Of the 65 patients included in this study, 55% met the composite inflammatory endpoint, while 29% had a second attack during the follow-up period. Every 25 nmol/l higher 25-hydroxyvitamin D level was associated with a 7.8 mL higher gray matter volume ($p=0.025$). A trend was noted for an inverse association between vitamin D levels and the composite endpoint of at least three new brain T2 lesions or at least one relapse within the first 12 months.

Conclusion: This study of patients with early CIS found that increased levels of 25-hydroxyvitamin D are associated with preserved gray matter volume.

Mowry, E., et al. Vitamin D in Clinically Isolated Syndrome: Evidence for Possible Neuroprotection. **Euro J of Neurol.** 2016, Feb; 23(2): 327-332.

OPIOID PRESCRIPTION AFTER NONFATAL OVERDOSE

Treatment of chronic, noncancer pain with opioids has increased dramatically in past decades. While deaths due to opioid overdose are closely tracked, there has been no prior analysis of continued prescribing patterns for persons who have suffered a nonfatal overdose. This retrospective, cohort study was designed to characterize opioid prescription patterns after an overdose among patients with long-

term opioid therapy for noncancer pain.

Medical information was obtained from a database of a commercial US health insurer. From this database were identified 2,848 adult patients presenting to a hospital setting with an overdose due to prescription opioid or heroin use between 2000 and 2012. The patients were followed from 90 days prior to overdose until age 65, a second overdose, disenrollment from the insurance plan, two years after the first overdose or the end of the study. The primary outcome measure was daily opioid dosage, as measured by the morphine-equivalent dosage (MED).

Over a median follow-up of 299 days, 91% of the patients continue to receive opioid prescriptions following the overdose. The MED ranged from 152 to 164 mg until the week prior to the overdose, when the dosage increased rapidly, peaking at 187 mg MED on the day before the overdose. After the overdose, the MED typically decreased to a mean of 118 mg MED, with 30% of the patients changing their primary prescriber following the overdose. Of the patients followed, seven percent had a second overdose within the follow-up time frame.

Conclusion: This study of patients presenting to a hospital setting for an overdose of opioids found that the majority continued to receive opioid prescriptions following the overdose.

Larochelle, M., et al. Opioid Prescribing after Nonfatal Overdose in Association with Repeated Overdose. *Ann Intern Med.* 2016, Jan 5; 164(1): 1-9

SYSTEMIC LUPUS ERYTHEMATOSUS MORBIDITY AND SMOKING

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting 40 to 200 per 100,000 persons throughout the world. While survival among patients with SLE has improved in the last decade, concern is increasing regarding cumulative damage by SLE. As smoking has been shown to impact the severity of SLE flares, this study evaluated the association between smoking and morbidity of SLE, as measured by the Systemic Lupus International Collaborating

Clinics/American College of Rheumatology Damage Index (SDI).

Subjects were 105 patients with SLE who were receiving oral corticosteroids and hydroxychloroquine as prescribed by their personal physicians. Data were obtained through questionnaires and a medical chart review, with data collected including patient characteristics and tobacco exposure. An SDI score was obtained, with patients divided into categories of tobacco exposure based upon smoking history.

Among the subjects, 66 had no smoking exposure and 39 had some smoking exposure, including 28 former smokers, 8 current smokers and 3 secondhand smokers. Among the 74 patients with an SDI score of greater than zero, 42 had never been exposed to smoking. Among those with an SDI score of zero, 24 (77.4%) were never smokers. The risk reduction of progressing to an SDI score of greater than zero was 22% among those never exposed to tobacco as compared to those who were ever exposed to tobacco.

Conclusion: This study of patients with lupus found that tobacco smoking is significantly associated with chronic damage and morbidity.

Montes, R., et al. Smoking and Its Association with Morbidity and Systemic Lupus Erythematosus, Evaluated by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. *Arthr Rheum.* 2016, February; 68(2): 441-448.

INTRA-ARTERIAL THERAPY AND INFARCT VOLUMES

The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) is a multicenter, randomized, controlled trial assessing endovascular treatment as compared with guideline based standard of care. Using data from that study, the authors sought to determine the efficacy of endovascular therapy in patients with acute ischemic stroke and proximal anterior circulation occlusion.

Subjects presenting within 12 hours of stroke onset with pre-specified neurovascular imaging criteria were studied. All underwent follow-up imaging at 24 and 48 hours

from stroke symptom onset. The data were reviewed for differences in stroke volume between treatment groups (endovascular and standard of care) and between subjects who did and who did not achieve early recanalization.

The median post-treatment infarct volume in all subjects was 21 mL, with the median infarct volume in the endovascular group of 15.5 mL and that in the control of 33.5 mL ($p < 0.01$). Early recanalization occurred in 72% of those in the endovascular group and 31% in the control group. Baseline NIHSS, Alberta Stroke Program Early CT score [ASPECTS], and recanalization status were independently associated with posttreatment infarct volume ($p < 0.01$ for all comparisons).

Conclusion: This study, using data from the ESCAPE trial showed that endovascular treatment among subjects with acute ischemic stroke and proximal anterior circulation occlusion is associated with smaller infarct volumes.

Al-Ajlan, F., et al. Intra-Arterial Therapy and Posttreatment Infarct Volumes. Insights from the ESCAPE Randomized, Controlled Trial. *Stroke.* 2016, March; 47(3): 777-781.

LEVODOPA-CARBIDOPA INTESTINAL GEL FOR ADVANCED PARKINSON'S DISEASE

Among patients with Parkinson's disease (PD), long-term, oral levodopa therapy is often associated with motor fluctuations, resulting from alterations in the plasma concentration of levodopa. To overcome these fluctuations, various therapeutic modalities have been developed. With the exception of deep brain stimulation, these therapies have failed to demonstrate significant long-term safety and efficacy profiles among patients with advanced PD. This Middle Eastern study assessed the effect of levodopa-carbidopa intestinal gel (LCIG) monotherapy on patients with PD.

Subjects were 20 to 80 years of age, presenting with advanced PD with motor fluctuations and non-motor symptoms. All patients were hospitalized and underwent a nasoduodenal tube insertion with levodopa-carbidopa intestinal gel infusions. These infusions were divided into a morning bolus and a

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continuous hourly dose, with these based on the equivalent oral medications previously used. The on-time, off-time and LCIG doses were recorded. Outcome measures included the unified PD scale (UPDRS III), non-motor symptoms scale (NMSS) and PD questionnaire-8 (PDQ-8).

During follow-up, the mean off-time, UPDRS-III, NMSS and PDQ-8 score improvements were significantly better after the gel infusion therapy than before.

Conclusion: This study of patients with PD found that levodopa-carbidopa intestinal gel infusion monotherapy can significantly improve time-off, reduce levodopa-induced dyskinesia and improve nonmotor symptoms and quality of life among patients who are inadequately responding to traditional oral therapy.

Bohlega, S., et al. Levodopa-Carbidopa Intestinal Gel Infusion Therapy in Advanced Parkinson's Disease: Single, Middle Eastern Center Experience. *Euro Neurol.* 2015, December 1; 74(5-6): 227-236.

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