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TANEZUMAB FOR CHRONIC LOW BACK PAIN

Given growing evidence that nerve growth factor (NGF) is a promising target for the treatment of patients with chronic low back pain (CLBP), this study assessed the effect of tanezumab, a monoclonal antibody targeting NGF, for the treatment of patients with CLBP.

This randomized, double-blind, controlled study was completed at 191 sites in eight countries. Subjects were patients 18 years of age and older with axial predominant, recalcitrant CLBP of three or more months' duration. All had a history of inadequate response to at least three different categories of standard care analgesics. The participants were randomized to receive oral tramadol, titrated to a maximum of 300 mg per day, tanezumab, 10mg or 5mg, administered subcutaneously every eight weeks, or subcutaneous and/or oral placebos. Treatment efficacy was characterized by low back pain intensity (LBPI) and scores on the Rowland Morris Disability Questionnaire (RMDQ).

Data were completed for 1,825 patients. Compared to placebo, those treated with tanezumab 10 mg (but not 5mg) reported significantly improved LBPI at 16 weeks (p=0.028). The proportions of patients with a 50% or greater improvement in LBPI at week 16 were 37.4% in the placebo group, 43.3% in the tanezumab 5 mg group and 46.3% in the tanezumab 10 mg group (tanezumab 10 mg vs. placebo; p=0.01). Those receiving tanezumab 10 mg also demonstrated greater improvement in RMDQ disability scores, as compared to subjects receiving the placebo (p=0.002). The tramadol group was found to have improved low back pain intensity, as compared with placebo, but only at weeks one and eight.

Conclusion: This double-blind, randomized, placebo-controlled trial involving patients with recalcitrant, chronic low back pain, found that subcutaneous tanezumab 10mg significantly reduced pain and improved function after 16 weeks of treatment.

Markman, J., et al. Tanezumab for Chronic Low Back Pain: A Randomized, Double-Blind, Placebo and Active-Controlled, Phase 3 Study of Efficacy and Safety. **Pain.** 2020, September; 161 (9): 2068-2078.

REGULAR DENTAL VISITS AND FUNCTIONAL DISABILITY

Previous studies have indicated that a decline in maximum occlusal force and a smaller number of remaining teeth are associated with a higher risk of incident functional disability. This study explored the association between regular dental visits at baseline and incident functional disability in community dwelling, older adults.

Baseline questionnaires were distributed in 2014 to adults, ages 65 and older. The baseline questionnaire queried respondents whether they had had regular dental visits for treatment and/or prevention during the prior 12 months. Functional disability was assessed using information from the public long-term care insurance (LTCI) certification, a mandatory social insurance system that subsidizes nursing care services for disabled older individuals. The researchers followed 9,352 persons who did not have a functional disability at baseline. Of these, 8,877 were followed until the end of the study in November of 2016. Covariates included age, gender, socioeconomic status, health status, body mass index, lifestyle factors and physical and mental functioning.

The proportion of respondents with no disability, mild disability, and severe disability at the follow-up survey were 92.2 %, 6.0 %, and 1.8 %, respectively. Those who had had regular dental visits were more likely to have a higher education, to have normal body mass index and to have practiced daily brushing. In an analysis controlling for all covariates, a history of regular dental visits at baseline was associated with a lower risk of incident severe disability (OR 0.65), but not the incidence of mild disability (OR 0.96).

Conclusion: This study of community dwelling older adults in Japan found that regular dental visits were associated with a decreased incidence of severe disability at follow -up.

Tomiola, K., et al. Regular Dental Visits May Prevent Severe Functional Disability: A Community Based, Prospective Study. **Arch Gerontol Geriatr.** 2020, May-June;88:104019.

BIOMARKERS IN TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is a recognized risk factor for late-life neurodegeneration. The mechanism of this degeneration is attributed to traumatic axonal injury (TAI). Given recent advances in immunoassay technology, serum measurements of TBI-related markers can now be made of tau, neurofilament light (NfL), quantified glial fibrillary acidic protein (GFAP), a marker of astrogliosis and ubiquitin C-terminal hydrolase- L1 (UCH-L1), a cytosolic neuronal protein. This study assessed the utility of these markers in the management of subacute and chronic TBI.

This prospective study enrolled patients with subacute and chronic TBI between 2011 and 2019. Blood samples were collected for analysis of NfL, GFAP, tau and UCH-L1. In addition, MRIs were obtained with volumetric analysis and diffusion tensor imaging. The primary outcome measures were changes in the biomarkers from 30 days to five years post-TBI.

Subjects were 162 patients with TBI at a mean of seven months after injury and 16 healthy controls. At enrollment, increased serum NfL concentrations were significantly related to worse GOS-E scores (p=0.0019) and DTI measures of

white matter integrity ($p<0.001$). Serum NfL distinguished patients with TBI from controls at 30, 90 and 180 days with high accuracy. The other biomarkers were not significantly related to GOS-E scores. Longitudinally, serum NfL measured at 180 days predicted white matter volume loss at one year ($p=0.001$). Increased concentrations of NfL and GFAP at enrollment were significantly related to MRI brain volumes and results of DTI measures of TAI.

Conclusion: This study of patients with traumatic brain injury found that neurofilament light is a highly sensitive marker for following patients with subacute and chronic traumatic brain injury.

Shahim, P., et al. Time Course and Diagnostic Utility of NfL, Tau, GFAP and UCH-L1 in Subacute and Chronic TBI. **Neurol.** 2020, Aug 11; 95(6): e623-e636.

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NEUROFILAMENT LIGHT AS A BIOMARKER IN PARKINSON'S DISEASE

A promising biomarker in neurodegenerative diseases is the neurofilament light (NfL) chain protein, which provides a sensitive measurement of neuroaxonal damage. This study investigated whether the severity of Parkinson's disease (PD) is related to NfL levels, and whether NfL levels are useful in predicting survival.

Subjects were within a defined geographic area of Sweden, identified between January 1, 2004, and April 30, 2009, all diagnosed with new onset idiopathic PD. The participants were followed prospectively, undergoing annual physical exams and testing including the Unified Parkinson's Disease Rating Scale (UPDRS) Part III score, the Bradykinesia and Axial Symptom subscores, and the Timed Up and Go Test. The assessments also included MRI and SPECT scans. For comparison, control participants were chosen who were age and gender matched. After inclusion, the participants were followed for 8.5 to 13.5 years.

The cerebral spinal fluid NfL concentration correlated positively with motor symptom severity. After adjustment for age and sex, for all comparisons, a higher NfL concentration correlated positively with the total UPDRS Part III score, the bradykinesia and axial symptom subscores, Timed Up and Go Test results and the severity of hyposmia. Higher NfL concentrations also correlated with a shorter survival. Those with concentrations of above the median of 3 mg/L had a higher risk of death during follow up, with an odds ratio of 5.8.

Conclusion: This study found that NfL is a biomarker of disease severity with prognostic values for survival in Parkinson's disease.

Backstrom, D et al. NfL as a Biomarker for Neurodegeneration and Survival in Parkinson's Disease. **Neurol** 2020, August; 95(7): e827-e838.

SKIING AND SNOWBOARDING INJURIES

Previous studies have reported on differences in injury patterns between skiers and snowboarders. Noting changes in demographics, as well as equipment used by skiers and snowboarders, the authors sought to describe and compare injury patterns between skiers and snowboarders over the five years ending in 2017 at one Colorado resort.

This retrospective study was conducted at Winter Park resort, including those who received an evaluation and definitive diagnosis at the medical clinic of the ski resort. In addition to injury information, data gathered included age, sex, helmet use, injury mechanism and disposition. Researchers reviewed 7523 records excluding 1128 for being unrelated to skiing or snowboarding.

From the demographic data, skiers were found to be older with an average age of 34.3 years compared to 23.2 years for snowboarders. Skiers most commonly injured their lower extremities (46.1%) and sustained sprains/strains (33.9%) while snowboarders most commonly injured their upper extremities (62.3%) and sustained fractures (45.6%). The modal injury of skiers was knee ligament sprains accounting for 20.5% of their injuries, with wrist fracture the modal injury of snowboarders at 25.7%.

Conclusion: This retrospective study of injuries at one Colorado ski resort found that skiers tend to injure the lower body and sustain sprains or strains, while snowboarders injure their upper extremities and sustain fractures.

Pierpoint, L., et al. A Comparison of Recreational Skiing and Snowboarding Related Injuries at a

Colorado Ski Resort, 2012/2013-2016/2017. **Res Sports Med:** 2020, 28(3): 413-425.

SINGLE HIGH MOLECULAR WEIGHT VERSUS TRIPLE LOW MOLECULAR WEIGHT HYALURONIC ACID INJECTIONS FOR KNEE OSTEOARTHRITIS

For the treatment of osteoarthritis (OA) of the knee, many international scientific associations have recommended intra-articular hyaluronic acid injections as an option for knee OA treatment. This study compared the efficacy and safety of a single dose of cross linked high molecular weight hyaluronic acid (HMW-HA) with that of three injections of low molecular weight hyaluronic acid (LMW-HA) for the treatment of OA of the knee.

Subjects were 90 patients 45 to 75 years of age with symptomatic knee OA. Eligible patients had Kellgren and Lawrence scores of II to III. The participants were randomized to receive HMW-HA in a three mL prefilled syringe (60 mg of sodium hyaluronate) or three, weekly sessions of LMW-HA injections using a two mL prefilled syringe (20 mg of sodium hyaluronate). After the injections, the subjects were engaged in an exercise therapy protocol, including isometric strengthening progressing to closed chain isotonic exercises. All were assessed using the Visual Analogue Scale for Pain, the Lequesne index and the Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire.

Compared with baseline measurements, significant improvements were noted in both treatment groups on all outcome measures, including pain, stiffness, function, and ADLs ($p<0.001$ for all). No significant difference was seen between treatment groups on any of the test or subtest scores except the WOMAC stiffness, with improvement statistically superior in the LMW-HA group at the second month follow-up ($p=0.021$).

Conclusion: This study of patients with osteoarthritis of the knee found that a single injection of high molecular weight hyaluronic acid was equal in effect to that of three, weekly injections of low molecular weight heparin with follow-up up to six months.

Bahrami, M., et al. Efficacy of a Single High Molecular Weight versus Triple Low Molecular Weight Hyaluronic Acid Intra-Articular Injection among Knee Osteoarthritis Patients. **BMC Musculoskel Dis.** 2020. doi.org/10.1186/s12891-020-03577-8.

ARTHROSCOPIC PARTIAL MENISCECTOMY FOR DEGENERATIVE MENISCAL TEAR

Arthroscopic partial meniscectomy (APM) is one of the most common orthopedic surgical procedures in the United States. Recent data suggests that APM is associated with an increased risk of progression of knee osteoarthritis (OA) and the subsequent need for further surgery, including knee replacement. This study further assessed the association between APM and OA of the knee.

The Finnish Degenerative Meniscus Lesion Study (FIDELITY) was a multicenter, randomized, placebo-controlled trial including patients with degenerative meniscal tears, 35 to 65 years of age. All underwent diagnostic arthroscopy, and then, during surgery, were randomly assigned to undergo either APM or placebo surgery. The subjects, all caregivers and those assessing the outcomes were held blind to the treatment group assignment. Subjects completed questionnaires at two, six, 12, 24, 36, 48 and 60 months postoperatively. The primary outcome measures were the Western Ontario Meniscal Evaluation Tool (WOMET), the Lysholm Knee Score and knee pain after exercise, all assessed at 60 months post-surgery.

Five years after surgery, 48 of 67 subjects in the APM group (72%) and 44 of 74 in the placebo surgery group (60%) had at least a one grade progression in radiographic knee OA. There were no significant differences in WOMET, Lysholm or knee pain scores between the groups. In both groups, most participants reported satisfaction with the procedure, including 78% in the APM and 84% in the placebo group.

Conclusion: This study of middle -age patients with degenerative medial meniscal tears found that arthroscopic partial meniscectomy resulted in a greater risk for progression of radiographic osteoarthritis, as compared with placebo surgery.

Sihvonen, R., et al. Arthroscopic Partial Meniscectomy for a Degenerative Meniscus Tear: A Five-Year Follow-Up of the Placebo-Surgery Controlled FIDELITY (Finnish Degenerative Meniscus Lesion Study) Trial. **Br J Sports Med.** 2020; doi:10.1136/bjsports-2020-102813.

KRILL OIL, ASTAXANTHIN, AND HYALURONIC ACID FOR PAIN

For the treatment of osteoarthritis (OA), current pharmacologic treatments serve to alleviate symptoms but often do not reverse or slow the degenerative process. This animal study evaluated the anti-arthritic effects of a mixture of krill oil, hyaluronic acid, and astaxanthin for treatment of OA of the knee.

Adult, male Sprague Dawley rats underwent an OA induction by injections into the right hind knees with either three mg of MIA or saline control. The animals were randomized into six groups of eight rats, including a normal sham control (Sham), an MIA-OA induced control (MIA), a positive control to receive the Cox-2 inhibitor Celecoxib (PC), and groups treated with daily oral supplements including 25 mg/kg(S-25), 50 mg/kg(S-50) and 100 mg/kg (S-100). The supplements contained 70% krill oil, 7% *Haematococcus pluvialis* extract, and 7% sodium hyaluronate, along with 16% various excipients. The supplements began seven days before induction of OA, and continued for 21 days after. The comparison of the weight-bearing distributions between the postoperative and Sham group limbs were determined as an indicator of pain. The animals were then euthanized, with the knees dissected to evaluate for structural cartilage damage, proteoglycan loss, and DNA. Serum levels were measured for levels of the pro-inflammatory cytokines, tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), and the cartilage degeneration mediators cartilage oligomeric matrix protein (COMP) and C-telopeptide of type II collagen (CTX-II).Outcome measures included pain behavior (weight bearing symmetry), cartilage damage scored with a modified Mankin score, and serum marker levels.

The weight bearing balance of the hind-paws of the PC, S-50 and S-100 groups returned to near that of the Sham group. Also, compared to the MIA group, significantly better Mankin scores were noted in the PC and all supplement groups ($p<0.05$ for all comparisons). In the supplement and PC groups, the serum levels of pro-inflammatory cytokines, when

compared to the MIA group, were significantly decreased. Finally, the degradation products COMP and CTX-II, were significantly lower in the PC, S-50 and S-100 groups as compared to the MIA group.

Conclusion: This animal study demonstrated that a daily oral administration of a combination of krill oil, *Haematococcus pluvialis* extract, and sodium hyaluronate could reduce pain, cartilage damage, proteoglycan loss, pro-inflammatory cytokines, and cartilage degeneration mediators.

Park, M et al. Flexpro MD, A Combination of Krill Oil, Astaxanthin and Hyaluronic Acid, Reduces Pain Behavior and Inhibits Inflammatory Response in Monosodium-Induced Osteoarthritis in Rats. **Nutrients**.2020, 12(4):956. Https:// Doi.Org/10.3390/Nu12040956.

CROSSFIT TRAINING AND INJURIES

As a training modality, high intensity functional training (HIFT), more commonly known as CrossFit training, merges the components of high intensity exercise and functional movements. This study was designed to better understand the risk of injury associated with engagement in CrossFit.

Subjects were 3,049 individuals reporting participation in a CrossFit sanctioned event between 2013 and 2017. Surveys were distributed, asking for information including demographics, training sites and frequency of participation in CrossFit training, including number of workouts per week. The surveys also requested a history of injuries occurring over the prior year while participating in CrossFit training.

Among those completing questionnaires, 16% reported an injury, with no significant difference between those who competed in CrossFit events and those who did not. Logistic regression analysis revealed that those with less than six months of CrossFit training had a greater risk of injury, as compared to those with at least five years of participation (OR 1.82). Overall, those with under one year of experience, and those training fewer than three days per week had an increased risk of injury, as compared to those with over three years of participation and training over five days per week (25% and 19% respectively).

Conclusion: This study of CrossFit training found an injury rate of 0.21 to 1.30 injuries per 1,000 hours of training, with a shorter duration of participation associated with a greater risk of injury.

Feito, Y., et al. Breaking the Myths of Competition: A Cross-Sectional Analysis of Injuries among Crossfit Training Participants. **BMJ Open Sport Exer Med.** 2020. .doi.org/10.1136/bmjsem-2020-000750.

PHOTOBIOMODULATION COMBINED WITH STATIC MAGNETIC FIELD FOR MUSCLE PERFORMANCE

Photobiomodulation therapy refers to the application of electromagnetic radiation to biological tissues using low-power lasers and light emitting diodes, inducing photochemical reactions in cells, leading to an increased mitochondrial ATP production. Static magnetic fields (sMF) have also been shown to affect biological processes, with some reporting effects including increased ATP production and reduced oxidative stress. This study assessed the effect of combining these interventions (PBMT-sMF) on markers of muscle performance and recovery.

This randomized, placebo controlled, clinical trial involved 30, sedentary males between 18 and 35 years of age. The subjects were randomized to one of three groups; *a placebo group*; with placebo PBMT-sMF bilaterally to the anterior thigh muscles of both lower limbs, *a local group*, with active PBMT-sMF to the anterior thigh muscles of the exercised lower limb and placebo PBMT-sMF to the nonexercised limb, *a non-local group* with active PBMT-sMF to the anterior thigh muscles of the nonexercised limb.

Blood samples were collected to assess creatine kinase enzymatic activity and blood lactate. Delayed onset muscle soreness (DOMS) was evaluated with a visual analog scale, and repeated for up to 72 hours. A maximum voluntary contraction (MVC) test was performed at baseline, immediately after the eccentric exercise to fatigue protocol, and at 1, 24, 48 and 72 h after protocol completion. The primary outcome variable was MVC, and the secondary outcomes were CK activity, blood lactate and DOMS.

The results of the MVC tests revealed a better peak torque in the local group at all time points after the eccentric exercise protocol ($p<0.05$). The outcomes observed in the non-local group were similar to those in the placebo group for all variables. The changes in creatinine kinase activity and blood lactate levels were significantly lower in the local group than in the other groups ($p<0.05$ for both comparisons).

Conclusion: This study of photobiomodulation combined with a static magnetic field found that this combined intervention improved performance and reduced muscle fatigue when applied directly to the muscles involved in the activity.

Machado, C., et al. Does Photobiomodulation Therapy Combined with Static Magnetic Field (PBMT-sMF) Promote Ergogenic Effects Even When the Exercised Muscle Group Is Not Irradiated? A Randomized, Triple-blind, Placebo-controlled Trial. **BMC Sports Sci, Med Rehab**. 2020. 12;49: 1-13.

PROBIOTICS, MUSCLE SORENESS, AND SLEEP QUALITY

In a previous study, the authors evaluated the relationship between the intestinal microbiome, probiotics and resistance to respiratory and gastrointestinal infections in elite Rugby players. In that study, correlations were found between the microbiome and muscle soreness, motivation, leg heaviness, and sleep quality and quantity. This study was designed to better understand the relationships among certain species within the microbiome and sleep, motivation and muscle soreness.

Subjects were 19 elite male rugby players. All participants provided subjective ratings of sleep quantity, sleep quality, motivation, muscle soreness and leg heaviness twice weekly. A saliva sample was collected to measure melatonin and C -reactive protein twice a week. Subjects were randomized to receive a placebo or a capsule containing probiotics, including 60 billion viable bacterial species from the genera Lactobacillus, Bifiodbacterium and Streptococcus. During team travel, to prevent travelers' diarrhea, players were given 250 mg of the yeast *Saccharomyces boulardii.*

Over the course of the 17-week intervention, self-reported muscle soreness was significantly lower in the probiotic group than in the placebo group ($p<0.0001$). Ratings of leg heaviness were also lower in the probiotic group, as compared with the placebo group ($p<0.0001$). As self

-reported muscle soreness scores and salivary CRP concentrations increased, sleep quantity, quality and motivation scores decreased.

Conclusion: This study of elite Rugby players found that supplementation with certain probiotics reduced self-perceived muscle soreness and leg heaviness.

Harnett, J., et al. Probiotic Supplementation Elicits Favorable Changes in Muscle Soreness and Sleep Quality in Rugby Players. **J Sci Med in Sport.** 2020. doi.org/10.1016/j.jsams.2020.08.005.

DIRECT CURRENT STIMULATION AND EPISODIC MEMORY IN THE COGNITIVELY IMPAIRED

Previous studies have suggested that transcranial direct current stimulation (tDCS) can improve episodic memory performance in the healthy aging population. This pilot study was designed to determine the effect of tDCS on those with mild cognitive impairment (MCI) or early Alzheimer's Disease (AD).

Subjects were 12 patients diagnosed with AD and 16 with MCI. Baseline data included age, gender and education level. In a double-blind, sham controlled, between subjects design, the participants were randomly assigned to a single session of sham or to real tDCS applied during a verbal episodic memory task. The tDCS was applied with the anode over the left dorsolateral prefrontal cortex and the cathode over the contralateral supraorbital region. Stimulation occurred at 1 mA for 20 minutes.

With tDCS, performance on the episodic memory task was better in patients with MCI and among those with higher education. For those with AD, the benefit of tDCS on the episodic memory task was found only among those who were less educated. In addition, those with better memory and higher education at baseline benefited from tDCS, while patients with worse memory benefited only if they were among the less educated.

Conclusion: This study of patients with mild cognitive impairment or Alzheimer's disease found that education is a moderating factor for the effects of transcranial direct current stimulation on memory performance.

Krebs, C., et al. Education Moderates the Effect of tDCS on Episodic Memory Performance in Cognitively Impaired Patients. **Brain Stim.** 2020, Sept-Oct; 13(5): 1396-1398.

ASPIRIN TO PREVENT DEMENTIA

Observational data have suggested that nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, may be neuroprotective, reducing cognitive decline and incident dementia. The Aspirin in Reducing Events in the Elderly (ASPREE) trial was designed to further understand the effect of low-dose aspirin on the incidence of Alzheimer's disease (AD) and mild cognitive impairment (MCI) in older individuals.

This randomized, controlled trial included healthy, community dwelling individuals 70 years of age or older. Subjects were randomized to receive either 100 mg of enteric coated aspirin per day or an identical appearing placebo. Cognitive tests were administered at baseline and at year one, then biannually up to year seven. Testing was performed with a cognitive battery including the Modified Mini-Mental State exam (3MS), the Hopkins Verbal Learning Test-Revised (HVLT-R) Delayed Recall task, the single letter (F) Controlled Oral Word Association Test (COWAT) and the Symbol Digit Modalities Test (SDMT).

Subjects included 9,525 in an aspirin group and 9,589 in a placebo group. The rates of incident dementia per 1,000 person-years were 6.7 events in the aspirin group and 6.9 in the placebo group. The rates of incident cognitive decline were 26.5 per 1,000 person years in the aspirin group and 25.6 per 1,000 person years in the placebo group. None of the differences reached statistical significance.

Conclusion: This prospective, placebo-controlled trial of aspirin therapy for individuals 70 years of age or over found no evidence that low-dose aspirin is useful for preventing dementia or mild cognitive impairment over five years.

Ryan, J., et al. Randomized, Placebo-Controlled Trial of the Effects of Aspirin on Dementia and Cognitive Decline. **Neurol.** 2020, July 21; 95 (3): e320-e331.

CARDIOVASCULAR RISK FACTORS AND COGNITION IN MIDLIFE

Risk factors for cognitive impairment and decline include cardiovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus, tobacco abuse and obesity. As longitudinal studies indicate that declines in several cognitive domains begin to emerge as early as midlife, this study assessed whether cardiovascular risk factors are associated with an accelerated cognitive decline in middle-aged adults.

Data were gathered as part of the multicenter longitudinal study, Coronary Artery Risk Development in Young Adults (CARDIA). Subjects were healthy and 18 to 30 years of age at enrollment in 1985 to 1986. This study reports on those who completed cognitive testing through year 25. Cognitive tests included the Digit Symbol Substitution Test (DSST) to assess processing speed and executive function, the Stroop Test to assess executive function and the Rey Auditory Verbal Learning Test (RAVLT) to assess verbal memory. At baseline, measures were made of exposure to cigarette smoking, obesity, diabetes mellitus, hypertension and high cholesterol. From these data were calculated the Framingham Coronary Heart Disease Risk Score. Other data collected in included demographic characteristics, physical activity, depressive symptoms, alcohol use and APOE e4 phenotype.

Data were available for 2,675 participants with a mean age of 50.2 years. The adjusted analysis revealed that the odds ratio (OR) for accelerated cognitive decline was increased with hypertension (OR 1.87), diabetes mellitus (OR 2.45) and smoking (OR 1.65). No significant effect was observed for high cholesterol or obesity. Those with a greater number of cardiovascular risk factors had a greater acceleration of cognitive decline.

Conclusion: This study of middle-aged, healthy adults found that cardiovascular risk factors are associated with an increased risk of accelerated cognitive decline.

Yaffe, K., et al. Cardiovascular Risk Factors and Accelerated Cognitive Decline in Midlife. The CARDIA Study. **Neurol.** 2020, August 18; 95 (7): e839-e846.

MEANING IN LIFE AND RISK OF COGNITIVE IMPAIRMENT

Studies have shown that individuals who perceive their lives as purposeful will perform better on tests

of memory and executive function in middle adulthood. This study was designed to understand whether the judgment of meaning in life is associated with the risk of cognitive impairment.

Data were obtained from the Survey of Health Aging and Retirement in Europe (SHARE), a prospective, cross-national study on health, socioeconomic status and social and family networks of individuals ages 50 years and older. Data collected from 2006 through 2010, served as a baseline assessment. Participants rated a single-item ("how often do you feel that your life has meaning?") on a scale ranging from one (often) to four (never). Cognition was measured with a memory recall task and an animal fluency task. Covariates included age, marital status and educational level.

With data from 22,514 participants, at a mean follow-up of 7.13 years, four percent of the cohort developed incident cognitive impairment. An adjusted analysis revealed that lower meaning in life scores were associated with a greater risk of impairment. Participants who reported never feeling meaning in their lives were at an approximately 75 % increased risk of impairment, as compared to participants who reported often feeling meaning in life (HR=1.75).

Conclusion: This multinational, prospective study found that a lack of a feeling of meaning in life is associated with an increased risk of incident cognitive impairment.

Sutin, A., et al. Meaning in Life and Risk of Cognitive Impairment: A Nine-Year, Prospective Study in 14 Countries. **Arch Gerontol Geriatr.** 2020; 88: May-June: 104033.

COMPRESSION THERAPY FOR CELLULITIS OF THE LEG

Compression therapy has been used to prevent recurrent cellulitis, although there are limited data to support this practice. This study was designed to determine the utility of compression therapy in reducing the recurrence of cellulitis of the legs in adults with chronic leg edema.

Subjects were patients with a history of two or more episodes of cellulitis in the same leg, and with edema lasting longer than two months in one or both legs. Those participants were randomized to receive leg compression therapy plus education concerning cellulitis prevention or education alone. Baseline data collected included demographics, leg volume, quality of life and medical history. All subjects were asked to report episodes of cellulitis when they occurred for up to three years. The primary outcome variable was the recurrence of cellulitis. Quality of life was assessed using the Quality of Life Measure for Limb Lymphedema (LYMQOL) and the EuroQol Group 5-Dimensions Three-Level Scale (EQ-5D-3L).

Data were completed for 84 subjects enrolled between June of 2017 and February of 2019. At the end of the trial, 15% of the compression group and 40% of the control group had an episode of recurrent cellulitis (p=0.002), with a relative risk of 0.37 favoring the compression group. At six months, two percent of the compression group and 12% of the control group had been hospitalized for cellulitis.

Conclusion: This study of patients with lower extremity edema found that compression therapy is more effective in lowering the incidence of recurrent cellulitis than is conservative treatment.

Webb, E., et al. Compression Therapy to Prevent Recurrent Cellulitis of the Leg. **N Engl J Med.** 2020, August 13; 383(7): 630-639.

FLUOXETINE AND FUNCTIONAL RECOVERY AFTER ACUTE STROKE

In 2011, the Fluoxetine for Motor Recovery after Acute Ischemic Stroke study found that the proportion of patients who were independent at three months was higher in a fluoxetine treated group than in a placebo group. This study was designed to determine the effect of fluoxetine on functional outcome at six months post-stroke.

Subjects were adults within two to 15 days of an acute stroke. Those participants were randomized to receive either a placebo or fluoxetine, 20 mg, daily for six months. At six months after randomization, the patients were assessed for functional status using the Modified Rankin scale (mRS), with other tests including the Stroke Impact Scale, the NIHSS tests of stroke severity, motor function and aphasia, the Montréal Cognitive Assessment for cognitive function, an assessment of depression using the DSM-IV and the Montgomery Depression Rating Scale. Subjects included 1,500 patients, of whom 750 were randomly assigned to fluoxetine and 750 to placebo.

At six months, there was no significant difference between the placebo and the fluoxetine group in mRS scores (p=0.42). In addition, the incidence rates of bone fractures and hyponatremia were higher in the fluoxetine group (p=0.0058 and p=0.0038, respectively), although fewer in the fluoxetine group were diagnosed with depression.

Conclusion: This study of patients with acute ischemic or hemorrhagic stroke found that fluoxetine for six months did not significantly improve modified Rankin Scale scores.

EFFECTS Trial Collaboration. Safety and Efficacy of Fluoxetine on Functional Recovery after Acute Stroke (EFFECTS): A Randomized, Double-Blind, Placebo Controlled Trial. **Lancet Neurol.** 2020, August 1; 19: 661-669.

POST-STROKE VAGUS NERVE STIMULATION

As vagus nerve stimulation (VNS) has been shown to release plasticity promoting neuromodulators, this study assessed the effect of combining active VNS with home exercises.

Subjects were patients with a history of unilateral ischemic stroke which had occurred up to five years prior to randomization. All had Fugl-Meyer upper extremity (FMA-UE) scores of between 20 and 50. These participants underwent implantation of a VNS device and were randomized to receive either active VNS or control VNS. After both groups underwent six weeks of in-clinic rehabilitation therapy, an individualized home exercise program was provided, with each session lasting two hours.

Outcome assessments were collected at six, nine and 12 months, with assessment tools including the FMA-UE, the Wolf Motor Function Test (WMFT), the Box and Block Test, the Nine Hole Peg Test, the Stroke Impact Scale (SIS), and a motor activity log.

At one-year follow-up, the FMA-UE scores increased by an average of 9.2 points (p=0.001), ranging from 10.8 points in the active group and 7.2 points in the cross-VHS group. In the active group, 73% demonstrated clinically meaningful improvement on the FMA-UE at one year. Significant improvement was also noted from baseline at one year on the WMFT, the SIS hand function and the motor activity log.

Conclusion: This unblinded study of patients with chronic stroke, receiving vagus nerve stimulation, found that this treatment improved

upper extremity function, with clinically meaningful improvement in 73% of the patients.

Dawson, J., et al. Vagus Nerve Stimulation Paired with Upper Limb Rehabilitation after Stroke: One-Year Follow-Up. **Neurorehab Neural Repair**. 2020; 34 (7): 609-6:15.

PROGESTERONE FOR MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

Several studies have shown that progesterone may be a potentially effective drug for patients with traumatic brain injury (TBI). This meta-analysis was designed to better understand the effectiveness of this medication for the acute treatment of patients with TBI.

A literature review was completed for studies of patients with moderate to severe TBI with treatments including progesterone. From this review, seven, randomized, controlled trials were included in the meta-analysis, with Glasgow Coma Scale (GCS) scores ranging from three to twelve. The primary outcome measure was good functional outcome, corresponding to a Glasgow Outcome Scale (GOS) score of 4-5, and a GOS -E of 5-8.

The rates of patients with a good functional outcome were 63.3% in the progesterone group and 43.3% in the control group. The relative risk was 1.48 in favor of the progesterone group ($p<0.00001$). The mortality rates were 18.1% in the progesterone group and 29.5% in the control group.

Conclusion: This meta-analysis found that progesterone at 1 mg/kg every 12 hours for five days could improve outcomes and reduced mortality among patients with moderate to severe traumatic brain injury.

Zang, J., et al. The Efficacy of Progesterone Every 12 Hours over Five Days in Moderate to Severe Traumatic Brain Injury: A Meta-Analysis of Randomized, Controlled Trials. **Clin Neurol Neurosurg**. 2020, November;198:106131.

CRYPTOGENIC NEUROPATHY

Of patients diagnosed with neuropathy, the diagnoses of at least 25% remain unknown. These have been termed cryptogenic sensory polyneuropathy (CSPN), with other terms including idiopathic neuropathy or small fiber sensory peripheral neuropathy. This study, the Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real Life Situations (PAIN-CONTRoLS), was designed to determine the best medication for the treatment of CSPN.

Eligible patients were 30 years of age or older with a diagnosis of CSPN. Those participants were randomized to receive one of four drugs, including nortriptyline 75mg, duloxetine 60mg, pregabalin 300mg or mexiletine 600mg. Doses were escalated weekly during the first four weeks as needed until the target doses were achieved. Study visits occurred at weeks four, eight and 12, with patients assessed using a single primary outcome measure combining efficacy rates and quit rates into a single "utility function". These findings were compared between drugs.

At 12-week follow-up, the percentage of patients who had quit the medication was lower among those receiving nortriptyline (38.1%) and duloxetine (37.3%), with the highest rate of discontinuation in the mexiletine group (58%). With "efficacious treatment", defined as at least a 50% pain reduction, pregabalin had the lowest efficacy (15.1%), with better rates noted for nortriptyline, 25.4%, duloxetine, 23.0%, and mexiletine, 20.3%. The utility functions were 0.81 for nortriptyline, 0.80 for duloxetine, 0.69 for pregabalin and 0.58 for mexiletine.

Conclusion: This study of patients with cryptogenic neuropathic pain found that, among the most commonly used medications, nortriptyline and duloxetine provided the best combination of pain reduction and fewer undesirable adverse effects.

Barohn, R., et al. Patient Assisted Intervention for Neuropathy: Comparison of Treatment in Real-Life Situations (PAIN- CONTRoLS). **JAMA Neurol**. doi:10.1001/ jamaneurol.2020.2590.

DANCE AND FRAILTY AMONG OLDER ADULTS

Studies have shown that frailty is a dynamic process that can be reversed. This study assessed the effects of dance intervention on frailty in older adults.

Subjects were nursing home residents 60 years of age or older with less than three hours of weekly physical exercise at baseline. Eligible residents were able to walk, and were without a neurologic or medical issue which would contraindicate participation. The participants who were assigned to an intervention group attended a dance program consisting of 40-minute dance sessions three times per week. Those subjects were taught Chinese square dancing, rated as being of mild to moderate intensity, using music with a strong rhythmic component. Those in a control group maintained their normal daily activities. Assessments were conducted at baseline and weeks six and 12 weeks by researchers held blind to the allocation. Frailty was measured with the Fried criteria.

Baseline assessments were completed by 66 individuals with a mean age of 81.8 years. Of these, 40% were considered to be pre-frail and 52% frail according to the Fried criteria. The prevalence of frailty decreased over time in the dance group as compared to the control group (OR 0.18; $p=0.002$). In the dance group, the mean frailty levels decreased by 0.69 at week six and by 1.06 at week 12, while increasing in the control group. As compared to the control group, the prevalence of slowness ($p=0.002$), weakness ($p=0.005$) and low physical activity ($p<0.001$) significantly improved in the dance group.

Conclusion: This study of nursing home residents found that Chinese square dancing for 40 minutes, three times per week, decreased frailty, reducing slowness, weakness and low physical activity.

Meng, X., et al. Effects of Dance Intervention on Frailty among Older Adults. **Arch Gerontol Geriatr.** 2020; 88: 104001.

FREMANEZUMAB FOR CHRONIC MIGRAINE

Fremanezumab is a monoclonal antibody which selectively targets calcitonin gene related peptide, with indications for the preventative treatment of migraine in adults. This study assessed the efficacy of this medication on the patient's health and quality of life.

The HALO CM phase III study included adult patients, 18 to 70 years of age. Those with chronic migraines were randomized to receive a placebo at weeks four and eight or fremanezumab at baseline, and then quarterly or monthly. All subjects were assessed with the Migraine Specific Quality of Life Questionnaire (MDQoL) and the EuroQol-5 standardized questionnaire of quality of life at baseline and up to week 12. In addition, all participants were asked to rate their current general health state on a 100-point visual analog

(Continued from page 2)

*Chloe McCloskey, M.D.
Ryan McLoughlin, M.D.
David Quan, M.D.
Univ. of Pennsylvania, Phila, PA

*Andrew Minkley, M.D.
Brian Cervoni, M.D.
Univ. of Washington, Seattle, WA

*Bonnie Weigert, M.D.
Delilah Kowalke, M.D.
Ashley Mohan, D.O.
Vincent Yaccarino, M.D.
Univ. Of Wisconsin, Madison, WI

*Austin Marcolina, D.O.
Annie Abraham, M.D.
Audrie Chavez, M.D.
Kegan Cunniff, M.D.
UTSouthwestern Med Ctr., Dallas, TX

*James Cole, M.D.
Adem Aktas, D.O.
Andrew O'Halloran, M.D.
Washington Univ., St. Louis, MO

scale (VAS), with higher scores indicating better health.

Data were analyzed for 1,034 patients with a mean age of 41 years, all with migraine diagnoses for the previous 20 years. Clinically meaningful and statistically significant improvements in mean scores were noted for each MDQoL domain from baseline to the end of treatment ($p<0.05$ for all comparisons). In addition, as compared with placebo, treatment with fremanezumab was associated with significantly greater improvement in overall health state, as measured by the EuroQol-5 VAS score, patient global impression of change, reduction in work productivity loss and general health ($p<0.05$ for all comparisons).

Conclusion: This study of patients with chronic migraine headaches found that either quarterly or monthly injections of fremanezumab, a monoclonal antibody, was significantly associated with improvement in migraine specific quality of life, global impression of change and work productivity.

Lipton, R., et al. Effect of Fremanezumab on Quality of Life and Productivity in Patients with Chronic Migraine. **Neurol**. 2020, August 18; 95(7): e878-e888.

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