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## ANIMAL PROTEIN INTAKE AND FUNCTIONAL CAPACITY

In the Japanese population, the percentage of individuals 65 years of age or older has increased from 10.3% in 1985 to 20.1% in 2005. While numerous factors related to functional decline in this population have been identified, few studies have examined the risk factors associated with the loss of high-level functional capacity. This study investigated the relationship between protein intake and the decline of high-level functional capacity in older, community dwelling, Japanese adults.

This longitudinal, community based, observational study included 2,614 healthy subjects 60 years of age or older identified in 1998. A validated, 141 item food frequency questionnaire was used to determine food intake levels at baseline and seven years later. From these questionnaires, participants were divided into four quartiles of intake of total, animal, and plant protein. Functional capacity was measured using the Tokyo Metropolitan Institute of Gerontology Index of Competence, which comprises three subscales, including social role, intellectual activity, and instrumental activities of daily living (IADLs).

During this seven-year study, 24.4% of the participants experienced a decline in high-level functional capacity. Multiple logistic regression analysis revealed that those in the highest quartiles of total protein and animal protein intake had a lower risk of future, high-level functional decline. No significant association was noted for plant protein intake. Looking further at sources of animal protein, multiple logistic regression analysis revealed that the highest quartile of fish intake was associated with a lower risk of future, high-level functional decline than were the lower quartiles (OR=0.63,  $p$  for trend=0.04), whereas meat intake was not

associated (OR=0.71,  $p$  for trend=0.10). Further analysis found a significant association between quartile of animal protein intake and future risk of high-level functional decline for men, but not for women.

**Conclusion:** This study found that higher level of animal protein intake, in particular fish, was associated with a lower risk of decline in high-level functional capacity in older men.

Imai, E., et al. Animal Protein Intake Is Associated with Higher Level Functional Capacity in Elderly Adults: The Ohasama Study. **JAGS**. 2014, March; 62(3): 426-434.

## FACIAL NERVE STIMULATION FOR ISCHEMIC STROKE

Currently available emergency treatments for ischemic stroke focus on removing or dissolving the occlusive blood clot. Another means of improving cerebral blood flow involves dilating the cerebral arteries. One method of doing so is facial nerve stimulation. However, accessing the facial nerve in the clinical setting is thought to be difficult. This study assessed the effect on cerebral blood flow of noninvasive stimulation of the facial nerve with magnetic energy.

This animal model involved 12 dogs receiving an autologous blood clot into the internal carotid artery, occluding the middle cerebral artery. An additional six dogs underwent brain hemorrhage with a puncture of the ICA. The dogs were randomly assigned to either a stimulation group or a control group. Those in the stimulation group received magnetic stimulation at the facial nerve for five minutes, beginning 30 minutes after the injury. Cerebral blood flow was noted before and after stimulation.

Cerebral blood flow was increased by facial nerve stimulation in the region of ischemia, with this

effect lasting 90 minutes or more after stimulation ceased. No such increase was found in control animals. In addition, blood flow to extra-cranial tissues was also increased, although this effect was seen only immediately post-stimulation. Among the animals with hemorrhagic strokes, no enlargement of the hematoma was noted. Cerebral blood flow did not change in this group, with a decrease in extra-cranial tissue flow.

**Conclusion:** This small animal study of ischemic stroke found that a modified, transcranial magnetic stimulator, applied to the facial nerve, produced a prolonged and sizable effect on cerebral blood flow and tissue perfusion. The authors call for further evaluation and clinical trials.

Borsody, M., et al. Effects of Noninvasive Facial Nerve Stimulation in the Dog: Middle Cerebral Artery Occlusion Model of Ischemic Stroke. **Stroke**. 2014, April; 45(4): 1102-1107.

## BIPHOSPHONATE FOR KNEE OSTEOARTHRITIS

Osteoarthritis (OA) is a growing cause of chronic disability and a major problem for health economies. Some research has focused on the effects of agents with potential for both cartilage and bone modifying benefits. Of the potential therapies, bisphosphonates have been studied, with mixed results. This study examined the effects of bisphosphonate use on symptoms and structural outcomes.

Data were obtained from the National Institute of Health (NIH) Osteoarthritis Initiative (OAI) cohort, which comprises data for persons 45 to 79 years of age. Subjects included those whose knees were scored as having joint space narrowing of Grade 2 or 3 on the Kellgren and Lawrence grading system, medial joint space width (JSW) of 2.5–5 mm,

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an osteophyte (medial osteophyte grade 1 and above) using the Altman atlas, and pain of 4–10 on a numeric rating scale. This cohort was divided into three subcohorts, including a Progression Group (persons with existing knee OA; n=1390), an Incidence Group (persons with risk factors for knee OA; n=3284) and a non-exposed Control Group (n=122). Biphosphonate use was calculated by classifying self-reported use of any biphosphonate and calculating the number of years used. Patients were followed for knee pain severity with the WOMAC questionnaire and knee radiographs, and for radiologic progression and joint replacements.

Numeric rating pain scale scores were reduced in the biphosphonate group at years two and three (p=0.001 and p=0.004, respectively), although not at year four. WOMAC pain scores were reduced over time, although the difference between the biphosphonate and control groups was not significant. Joint space width was reduced in both the users and the control group over time, with the incidence of progression lower in the biphosphonate group after three years (p=0.04).

**Conclusion:** This study found that the use of biphosphonates in patients with osteoarthritis of the knee may provide both symptomatic and structural benefits.

Laslett, L., et al. Effect of Biphosphonate Use in Patients with Symptomatic and Radiographic Knee Osteoarthritis: Data from the Osteoarthritis Initiative. *Ann Rheum Dis.* 2014, May; 73(5): 824-830.

### **AQUATIC THERAPY FOR CHRONIC LOW BACK PAIN**

Previous studies have demonstrated that exercise can improve pain, disability and quality-of-life among patients with chronic low back pain (LBP). This study assessed the effects of intensive aquatic therapy in sedentary adults with chronic LBP.

Subjects were between 18 and 65 years of age, all with self-reported LBP of at least 12 weeks' duration. The patients were divided into an intervention group, or to a waitlist control. The intervention group received a two month program of 40 sessions, five days per week, with no exercise for the control group. Each

session was 55 to 60 minutes long and included resistance and aerobic exercise. LBP was assessed at rest and during movement, using a visual analogue scale (VAS). Other outcome measures included the Spanish version of the Oswestry Low Back Pain Disability Questionnaire, as well as the Spanish version of the Short Quality Form Health Survey-36 (SF-36).

The total of 21 patients from the active group and 17 from the control group completed all aspects of the trial. Significant differences were noted between the active and control groups for improvement in VAS scores for pain at rest, flexion and extension, and for the Oswestry Disability Index (p<0.001), as well as the physical component of the SF-36 (p<0.001).

**Conclusion:** This study of patients with low back pain found that a two-month, intensive, aquatic therapy program, five times per week, decreased back pain and disability and improved scores on measures of quality of life.

Baena-Beato, P., et al. Aquatic Therapy Improves Pain, Disability, Quality-of-Life, Body Composition, and Fitness in Sedentary Adults with Chronic Low Back Pain. A Controlled, Clinical Trial. *Clin Rehab.* 2014, April; 28(4): 350-360.

### **AQUATIC THERAPY TREATMENT FOR SUBACUTE STROKE**

Successful therapeutic interventions for patients with stroke often emphasize early active and repetitive training. This study assessed the effect of a specific aquatic intervention strategy, Halliwick-Therapy, for patients with subacute stroke.

Subjects were adult patients with a first-ever stroke, at least two weeks after stroke onset. The treatment group received three Halliwick-Therapy pool sessions and two conventional physiotherapy sessions per week for two weeks. Approximately 15 minutes of each pool session was used for exercising rotational control, with 15 minutes of locomotion under various disturbances and changing water depths. The control group received five sessions of standard physiotherapy per week. The primary outcome measure was postural

stability, as assessed with the Berg Balance Scale. Secondary outcomes included measurements of functional reach, functional gait and functional mobility.

Fourteen patients were assigned to aquatic therapy and 16 to a control condition. Significant improvements were noted in both groups on both the primary and secondary measures. A higher portion of patients in the aquatic therapy group achieved clinically relevant improvements on the Berg Balance Scale than did those receiving standard treatment ( $p < 0.05$ ). The mean improvement in functional ambulation was significantly higher in the aquatic group than in the control group.

**Conclusion:** This study of patients with subacute stroke found that the Halliwick-Therapy method of aquatic therapy may be effective in improving postural stability and gait.

Tripp, F., et al. Effects of an Aquatic Therapy Approach (Halliwick-Therapy) on Functional Mobility in Subacute Stroke Patients: A Randomized, Controlled Trial. *Clin Rehab*. 2014, May; 28(5): 432-439.

### DOOR TO NEEDLE TIME FOR ISCHEMIC STROKE

Intravenous tissue plasminogen activator (tPA) has been found to reduce long-term disability in patients with acute ischemic stroke, although these benefits are highly time dependent. However, prior studies have demonstrated that less than one third of patients presenting with acute ischemic stroke in the United States are treated within the guideline recommended timeframe. This study sought to better understand the effect of door to needle time on clinical outcomes.

Data were collected as part of the Target Stroke Quality Improvement Initiative launched in January of 2010 to address the shortfall in providing timely acute ischemic stroke care. The primary goal of the initiative was to administer tPA to at least 50% of the patients with acute ischemic stroke within 60 minutes of hospital arrival. Strategies included prenotification of hospitals by emergency medical services personnel, activating the entire stroke team with a single call or page, rapid acquisition and interpretation of brain imaging, use of specific protocols and

tools, premixing tPA for high-likelihood candidates, a stroke team-based approach and rapid feedback to the stroke team regarding performance.

A total of 71,169 patients with acute ischemic stroke were identified for study analysis. The median age of the sample was 72 years, with 50.1% women. The median door to needle time for tPA administration for the pre-intervention period was 77 minutes, decreasing to 67 minutes in the post-intervention period ( $p < 0.001$ ). The percentage of patients with a door to needle time of 60 minutes or less increased from 29.6% to 53.3%. After the initiative, in-hospital mortality for patients with ischemic stroke was less likely ( $p < 0.001$ ), while discharge to home was more likely ( $p < 0.001$ ).

**Conclusion:** This study found that the implementation of a national quality improvement initiative resulted in improved timeliness of tPA administration, resulting in improved hospital mortality, decreased intracranial hemorrhage and increased discharges to home.

Fonarow, G., et al. Door to Needle Time for Tissue Plasminogen Activator Administration and Clinical Outcomes in Acute Ischemic Stroke before and after a Quality Improvement Initiative. *JAMA*. 2014, April; 23(30): 1632-1640.

### ENDOVASCULAR THERAPY FOR ACUTE ISCHEMIC STROKE

While intravenous thrombolysis (IVT) has been found to be an effective treatment for acute ischemic stroke (AIS), a high percentage of patients are left untreated due to contraindications or a delay the hospital arrival. Among alternative treatments are endovascular therapies including mechanical thrombectomy. This study was designed to further understand the efficacy of endovascular therapy (EVT).

This multicenter study included consecutive patients treated with endovascular therapy between January of 2011 and December of 2012. All patients with AIS, with no contraindications to IVT, were treated. Those refractory to, or ineligible for IVT, were preselected for EVT. Outcome measures included SICH, defined as the percentage of EVT patients who had developed a

symptomatic cerebral bleed 24 to 36 hours after the procedure, all-cause mortality at three months and functional independence, defined as a modified Rankin Scale score of two or less at three months.

Data were collected for 536 patients with AIS who underwent EVT. Of those, 90.5% had mechanical thrombectomy and 7.5% had a combination of pharmacological and mechanical approaches, while two percent had intra-arterial thrombolysis. Revascularization occurred in 73.9%, with 5.6% developing symptomatic intracerebral hemorrhages. Of the patients treated, 43.3% achieved a good functional outcome, while 22.2% died within 90 days. Revascularization was inversely associated with SICH and mortality rate ( $p < 0.001$  for both). Logistic regression analysis revealed that revascularization was the strongest independent predictor of both good and fatal outcomes. Beyond revascularization, hypertension and age of over 80 were independent deleterious factors.

**Conclusion:** This multicenter trial of patients with acute ischemic stroke found that, among those who did not qualify for tPA, endovascular therapy could improve revascularization, with 43.3% achieving a good functional outcome.

Abilleira, S., et al. Outcomes of a Contemporary Cohort of 536, Consecutive Patients with Acute Ischemic Stroke Treated with Endovascular Therapy. *Stroke*. 2014, April; 45(4): 1046-1052.

### PREDICTING OUTCOME AFTER EARLY BRAIN INSULT

Recent advances in neuroscience demonstrate that brain plasticity can facilitate changes in the brain in response to environment and experience. This study was designed to further understand the impact of age at the time of brain insult, as well as the influence of insult and environmental factors on cognitive and behavioral outcomes.

Children with a focal brain insult were identified from records at the Royal Children's Hospital in Melbourne, Australia, between 2005 and 2007. Participants were between the ages of 10 and 16 years at the time of assessment, with the insults

having occurred at least 12 months before the assessment. All had MRI evidence of focal pathology. Data collected included environmental factors and neuropsychological outcome measures. The outcomes were compared between those who had sustained an insult before the age of three and those sustaining the insult at a later age.

One hundred thirty-six participants were included in the analysis. Those in the early insult group were more likely to have seizures, and more likely to have had a brain insult mechanism that was developmental rather than traumatic. Those in the late insult group had higher Full Scale IQ scores at follow-up ( $p < 0.001$ ), as well as higher Verbal and Performance Scale IQ scores and greater executive function, with fewer behavior problems and better social function, than did those with an early insult.

**Conclusion:** This study of patients with focal brain insult found that those injured before the age of three had poorer outcomes than those injured at a later age.

Anderson, V., et al. Predicting Neurocognitive and Behavioral Outcome after Early Brain Insult. *Develop Med Child Neurol*. 2014, April; 56(4): 329-336.

### LARGE MIDDLE CEREBRAL ARTERY STROKE AND HEMICRANIOTOMY

Large middle cerebral artery (MCA) infarctions are associated with the development of massive brain edema, which may lead to herniation and early death. This condition has been described as malignant MCA infarction. Decompressive hemicraniotomy, combined with duraplasty, can prevent fatal internal displacement of brain tissue and herniation. This study was designed to test the outcome of early hemicraniectomy compared with intensive care unit (ICU) treatment among patients 61 years of age or older with malignant MCA infarction.

This prospective, randomized, controlled open trial included patients 61 years of age or older with a diagnosis of acute unilateral MCA infarction, involving at least two thirds of the MCA territory. Subjects were assigned to either treatment in the ICU or early hemicraniectomy. Data

were collected during hospitalization and at follow-up visits at six and 12 months. The primary outcome measure was a score of 0 to 4 on the modified Rankin scale at six months.

A total of 112 patients were randomized to the study. In the intention to treat sample, survival without severe disability occurred in 38% of the surgery group and 18% of the control group ( $p = 0.04$ ). The 12-month survival rates were 57% in the surgery group and 24% in the control group. The intention to treat analysis revealed that all secondary endpoints were significantly better in the surgery group than in the control group. This trial was discontinued for reasons of efficacy after reductions in deaths and severe disability had become significant.

**Conclusion:** This study of patients with extensive MCA stroke found that early hemicraniectomy can significantly improve survival, although most survivors had substantial disability.

Juttler, E., et al. Hemicraniectomy in Older Patients with Extensive Middle Cerebral Artery Stroke. *N Eng J Med*. 2014, March 20; 370(12): 1091-1100.

### VITAMIN D AS A PREDICTOR OF MULTIPLE SCLEROSIS ACTIVITY

Previous studies have demonstrated that low levels of vitamin D are associated with multiple sclerosis (MS) activity. This study was designed to determine whether vitamin D status, early in the MS disease process, influences the long-term course and progression of the disease.

Data were obtained from the participants of the Betaferon/Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) trial. Levels of 25 (OH) D were collected at baseline and at six, 12 and 24 months. The patients were followed for MS activity, with outcomes including time to definite diagnosis of MS, MS activity and MS progression. Assessments were made using the McDonald criteria (MDMS), the Poser criteria and radiologic progression.

Over five years' follow-up, conversion to MS was documented in 81.3% to MDMS and 46.6% to clinically definite MS (CDMS). The hazard of conversion decreased with increasing serum 25 (OH) D. Among

those with data at both six and 12 months, the hazard of conversion decreased by more than 50% for a 50 nmol/L increase in 25 (OH) D. The relative decrease in T2 lesion volume for a 50-nmol/L increase in 25 (OH) D was 20% per year ( $p < 0.001$ ). The annualized change in EDSS score was lower among patients with serum 25 (OH) D levels greater than or equal to 50 nmol/L, as compared with those with less than 50 nmol/L ( $p = 0.004$ ).

**Conclusion:** This study of patients with MS found that higher levels of vitamin D predicted a lower level of multiple sclerosis activity and disease progression over five years.

Ascherio, A., et al. Vitamin D as an Early Predictor of Multiple Sclerosis Activity and Progression. *JAMA Neuro*. 2014, March; 71(3): 306-314.

### VITAMIN D AND CAUSE-SPECIFIC DEATH

Supplementation with vitamin D has been shown to benefit skeletal conditions, with a growing body of evidence indicating that vitamin D may also reduce risks of a wide range of nonskeletal diseases. This study summarized the available evidence to determine associations of various 25-hydroxyvitamin concentrations with the risk of cause-specific mortality and quantified the effects of supplementation.

A literature search was completed using Medline, Embase and Cochrane databases. Observational cohort studies and randomized trials were considered for inclusion, which included data on associations of circulating 25-hydroxyvitamin D concentration with cause-specific or all-cause deaths in adults.

Of the studies reviewed, 95 met the inclusion criteria for the meta-analysis. For the primary prevention cohorts, pooled risk ratios comparing those in the bottom with the top third of the 25-hydroxyvitamin D concentrations were 1.25 for cardiovascular disease, 1.14 for cancer, 1.3 for other nonvascular, noncancer death and 1.35 for all-cause mortality. Each 10 ng/mL decline of 25-hydroxyvitamin D concentration was associated with a 16% increased risk of all-cause mortality. In studies focusing on vitamin D supplementation, no significant effect on mortality was

medication, Tripterygium Wilfordi Hook F, is at least as effective as MTX, while the combination of both was superior to MTX for the treatment of rheumatoid arthritis.

Lv, Q., et al. Comparison of Tripterygium Wilfordi Hook F with Methotrexate in the Treatment of Active Rheumatoid Arthritis. *Ann Rheum Dis.* doi:10.1136/annrheumdis-2013-204807

### HOME-BASED EXERCISES IN WOMEN WITH OSTEOARTHRITIS OF THE HAND

Hand osteoarthritis (HOA) has a high and increasing prevalence. In the Framingham Osteoarthritis Study, 16% of women and 8% of men ages 28 to 92 years had symptomatic hand OA. While many recommend exercise, including range of motion and strength, to address HOA, evidence of the efficacy of this intervention is sparse. This study was designed to better understand the effect of hand exercises in women with HOA.

Between February of 2011 and December of 2012, patients were screened for eligibility. Inclusion criteria were the diagnosis HOA, age 18 to 80 years, stable medications and a minimum of three, self-reported HOA activity limitations. All patients underwent radiographs of both hands. The participants were randomized to either engage in an exercise program or to receive information only. The primary outcome measure was change in activity performance, as assessed by The Patient Specific Functional Scale (PSFS) at three-months.

After three months, greater improvement was noted in the exercise group in PSFS scores ( $p < 0.001$ ). The number of participants who reached clinically relevant positive change, no change or clinically relevant negative change on the PSFS favored the exercise group ( $p < 0.007$ ). Significant differences in favor of the exercise group were founded for multiple secondary measures.

**Conclusion:** This study of women with hand osteoarthritis found that a hand exercise program is well tolerated and results in significant improvement in activity performance, strength, fatigue, and pain resolution.

Hennig, T., et al. Effect of Home-Based Hand Exercises in Women with Hand Osteoarthritis: A Randomized, Controlled Trial. *Ann Rheum Dis.* 2014; doi:10.1136/annrheumdis-2013-204808

### GLOBAL BURDEN OF LOW BACK PAIN

Low back pain (LBP) is the leading cause of activity limitation and work absence throughout much of the world. As a part of the Global Burden of Disease (GBD) 2010 study, the global burden of musculoskeletal disease conditions was estimated. This study reports on the findings for LBP.

LBP was defined as activity limiting pain that lasts for least one day. To determine prevalence, 170 published studies were identified. Surveys were then conducted in five countries for the GBD 2010 to establish disability weights. Those disability weights were applied to prevalence data to determine years lived with disability as a result of LBP.

The global, age standardized point prevalence of LBP in 2010 was 9.4%. Prevalence peaked at about 80 years of age. The prevalence was highest in Western Europe, with a mean of 15%, followed by North Africa/Middle East, at 14%, and lowest in the Caribbean, at 6.5%. Globally, out of 291 conditions studied, LBP was ranked as the greatest contributor to global disability, and sixth in terms of overall burden.

**Conclusion:** This global study of low back pain found that, in 2010, low back pain caused more years lost to disability than did any other condition.

Hoy, D., et al. The Global Burden of Low Back Pain: Estimates from the Global Burden of Disease 2010 Study. *Ann Rheum Dis.* 2014, June; 73:975-981.

### TRANSCRANIAL MAGNETIC STIMULATION FOR MOTOR LEARNING AFTER STROKE

Repetitive transcranial magnetic stimulation (rTMS) has been used to modulate local cortical excitability in a frequency dependent manner. This study was designed to determine whether 5 Hz rTMS over the primary sensory cortex, paired with skilled

motor practice, would result in improved motor learning.

Fifteen individuals with first-time, chronic (>six months post) stroke were randomized to either active or sham rTMS groups. On day one, the subjects were tested with a serial targeting task (STT), two-point discrimination, the Wolf Motor Function test, the Box and Block Test of manual dexterity (BBT) and resting motor threshold (RMT). The participants then received either rTMS or sham stimulation over the IL-S1, after which they underwent a motor practice set. Motor learning was assessed using the STT.

The treatment group demonstrated greater improvement than the sham group in STT performance, including response time ( $p < 0.0005$ ), peak velocity ( $p < 0.044$ ), cumulative distance ( $p < 0.044$ ) and cutaneous somatosensation ( $p = 0.007$ ). No significant effect was observed for measures of motor function or manual dexterity.

**Conclusion:** This study of patients with chronic stroke found that pairing skilled motor practice with 5Hz repetitive transcranial magnetic stimulation may enhance motor learning.

Brodie, S., et al. Five Hz Repetitive Transcranial Magnetic Stimulation over the Ipsilateral Sensory Cortex Enhances Motor Learning after Stroke. *Front Hum Neurosci.* March 21 doi: 10.3389/fnhum.2014.00143

### SILDENAFIL AND NEURONAL PROTECTION AFTER NEONATAL HYPOXIA-ISCHEMIA

Neonatal hypoxia - ischemia (HI) is one of the most common causes of severe neurologic handicap among children. The decreased cerebral blood flow during reperfusion in the first 12 to 24 hours indicates a poor prognosis, with perinatal asphyxia and hypoxia-ischemia encephalopathy. One option for enhancing the flow involves blocking cGMP degradation by phosphodiesterases (PDEs). This study was designed to test the effect of a potent phosphodiesterase-five inhibitor, sildenafil, in an animal model of neonatal hypoxia -ischemia.

This study used Sprague-Dawley rat pups. All animals underwent occlusion of the right common carotid artery, followed by 120 minutes of

found in older adults. When stratified by type of supplementation, D3 reduced all-cause mortality by 11%, while D2 had no effect.

**Conclusion:** This meta-analysis of studies concerning vitamin D and the risk of cause-specific death found an inverse association between circulating 25-hydroxyvitamin D concentrations and the risk of death, while supplementation with vitamin D3 reduced overall mortality among older adults.

Chowdhury, R., et al. Vitamin D and Risk of Cause-Specific Death: A Systematic Review and Meta-Analysis of Observational Cohort and Randomized Intervention Studies. *Br Med J*. 2014; 348: g1903.

### VITAMIN D AND CHANGES IN KNEE AND HIP PAIN

Vitamin D deficiency is common among individuals with widespread bone and muscle pain, although this association may be biased, in that illness often leads to lower sun exposure. This study assessed the association between serum 25 hydroxy vitamin D and changes in knee and hip pain.

Data were obtained from the Tasmanian older adult cohort, a population-based study including men and women 50 to 80 years of age in 2002. Baseline data were obtained over two years, including 25-hydroxy vitamin D levels, as well as pain assessments using the Western Ontario and McMaster University Osteoarthritis (WOMAC) index questionnaire. All participants underwent x-ray examinations of the hips and knees, with films scored according to the Osteoarthritis Research Society International Atlas. Follow-up data were obtained at an average of 2.6 years and five years later.

The prevalence of knee pain was 53% at baseline and 45% at five-year follow-up. Participants with moderate vitamin D deficiency experienced a greater worsening of total knee WOMAC pain scores over five years than did those above that level. The association with total hip WOMAC pain scores over 2.4 years did not reach statistical significance. When data were dichotomized, levels <25 nmol/l predicted incident or worsening pain according to total knee WOMAC scores, as compared with levels

above this. Similar patterns were present in hip pain, although these findings did not reach statistical significance.

**Conclusion:** This study suggests that a moderate vitamin D deficiency independently predicts change in knee pain over five years and, possibly, hip pain over 2.4 years.

Laslett, L., et al. Moderate Vitamin D Deficiency is Associated with Changes in Knee and Hip in Older Adults: A Five-Year, Longitudinal Study. *Ann Rheum Dis*. 2014, April; 73(4): 697-703.

### VECTOR BASED GENE THERAPY FOR PARKINSON'S DISEASE

A crucial pathological component of Parkinson's disease (PD) is the progressive deterioration of dopaminergic neurons in the substantia nigra pars compacta. As the disease progresses, levodopa therapy becomes less effective. Gene therapy approaches using lentiviral vectors have been suggested as an option due to their low immunogenicity and high efficiency. This study assessed the efficacy of a lentiviral vector-based gene therapy (ProSavin) in restoring local and continuous dopamine production.

All subjects had bilateral idiopathic PD and were 48 to 65 years of age, with disease duration of at least five years. Three dose levels of ProSavin were assessed. The vector was administered bilaterally into the striatum under general anesthesia. The primary endpoints were the number and severity of adverse events, and motor responses, as assessed with the Unified Parkinson's Disease Rating Scale (UPDRS), administered six months after vector administration. The participants were clinically assessed weekly during the first month and at one, two, three, six, 12 months.

Of the 15 patients followed, three received dose level I, six dose level II and six dose level III. Eight serious events were noted, and determined to be unrelated to the study drug. The most common drug related adverse events were increased on-medication dyskinesias, and on-off phenomena. The UPDRS motor scores were significantly improved as compared with baseline at six months and at 12 months in all 15 patients ( $p=0.0001$

for both). No significant differences were found among different dose cohorts.

**Conclusion:** This study found that a lentivirus vector-based gene therapy is safe, and can improve motor behavior in patients with Parkinson's disease.

Palfi, S., et al. Long-Term Safety and Tolerability of Prosavin, a Lentiviral Vector Based Gene Therapy for Parkinson's Disease: A Dose Escalation, Open Label, Phase 1/2 Trial. *Lancet*. 2014, March; 29(9923): 1138-1146.

### TRIPTERYGIUM WILFORDI HOOK F FOR RHEUMATOID ARTHRITIS

Tripterygium Wilfordi Hook F (TwHF) is a traditional Chinese medicine for the treatment of joint pain, edema and local inflammation. In China, this product is approved, and is often used to treat rheumatoid arthritis (RA). This study compared the efficacy and safety of this medication with that of methotrexate (MTX).

This open label, 24 week-trial included patients between the ages 18 and 65 years, each diagnosed with active RA. The subjects were randomized to receive oral TwHF 20 mg three times a day, MTX, beginning at 7.5 mg weekly and increased to 12.5 mg weekly or a combination therapy with both medications. The participants were assessed at weeks four, 12 and 24, with the primary efficacy endpoint being the portion of patients achieving the American College of Rheumatology criteria of at least 50% improvement (ACR50).

A total of 207 patients were enrolled in the study. The intention to treat analysis revealed that the proportions of patients achieving the ACR50 were 46% in the MTX group, 55.1% in the TwHF group and 76.8% in the combination group. A noninferiority test demonstrated a significant difference in efficacy between the two treatment medications ( $p=0.014$ ). Similar patterns were seen for multiple secondary outcome measures. A significant difference was noted between the combination therapy group and the MTX monotherapy group.

**Conclusion:** This study found that the traditional Chinese

hypoxia. The subjects were randomly assigned to receive a placebo or a single dose of sildenafil citrate at five or 10 mg per kilogram intraperitoneally. The animals were euthanized after 72 hours and seven days after the HI event. All were assessed by physiological parameters, by immunohistochemistry, myelin sheath assessment, and motor performance.

At seven days, the dose of 10 mg/kg of sildenafil significantly reduced brain tissue loss ( $p<0.01$ ), whereas the 5 mg/kg dose did not, when compared with placebo. The index of myelinated fiber density (ratio of the ipsilateral to the contralateral hemisphere) was found to be increased in sildenafil-treated animals (10 mg/kg) in both the cingulum ( $p<0.01$ ) and the external capsule ( $p<0.05$ ) when compared with placebo-treated subjects. Seven days after HI and sildenafil treatment, tissue loss was significantly reduced, and motor coordination recovered as compared to the controls.

**Conclusion:** This animal study of neonatal hypoxia - ischemia suggests that treatment with sildenafil citrate can increase cerebral blood flow and reduce cell damage, improving motor locomotion.

Charriat- Marlangué, C., et al. Sildenafil Mediates Blood Flow Redistribution and Neuroprotection after Neonatal Hypoxia - Ischemia. *Stroke*. 2014, March; 45(3): 850-856.

### C- REACTIVE PROTEIN AFTER LACUNAR STROKE

A number of research studies have demonstrated that inflammation plays a major role in atherosclerosis and cardiovascular disease. This study was designed to determine whether inflammatory markers predict recurrence after lacunar stroke

This study was nested within the ongoing Secondary Prevention of Small Subcortical Strokes (SPS3) that focused on secondary prevention of stroke recurrence in patients with small vessel ischemic strokes, or lacunes. The Levels of Inflammatory Markers in the Treatment of Stroke Study (LIMITS) involved the collection of plasma and serum samples at baseline and at one year with analysis of samples for inflammatory marker levels, including high sensitivity C-reactive protein

(hsCRP). The primary outcome measures were the recurrence of ischemic stroke and the combined outcome of major cardiovascular events, including recurrent ischemic stroke, myocardial infarction or vascular death.

Among the 1,244 patients followed, 83 recurrent ischemic strokes were documented, including 45 lacunar strokes, during a median of three years' follow-up. Compared with the bottom quartile of hsCRP, those in the top quartile were at increased risk of recurrent ischemic stroke, with an unadjusted hazard ratio of 2.54, and an adjusted (for statin use) hazard ratio of 2.32. Approximately 70% of the recurrent ischemic strokes were lacunes. The hazard ratio for lacunes among those in the highest compared with the lowest hsCRP level was 2.27.

**Conclusion:** This study of patients with recent lacunar stroke found that hsCRP may be useful in predicting those at risk for recurrent stroke.

Elkind, M., et al. C- Reactive Protein as a Prognostic Marker after Lacunar Stroke. Levels of Inflammatory Markers in the Treatment of Stroke Study. *Stroke*. 2014, March; 45(3): 707-.

### PHONOPHORESIS VERSUS ULTRASOUND FOR MYOFASCIAL PAIN

Various treatment methods have been used to address myofascial pain syndrome (MPS), to release trigger points and taut bands. Ultrasound (US) is commonly used to treat this disorder. Phonophoresis (PH) is used to increase skin absorption and the penetration of topically applied drugs. This study compared the effects of EMLA cream applied using phonophoresis, to those of US for the treatment of myofascial pain syndrome.

This randomized, single-blind study included 50 patients diagnosed with MPS involving the trapezius muscle. The subjects were randomized either to receive EMLA cream (2.5% lidocaine, 2.5% prilocaine) delivered with phonophoresis, or to an ultrasound group receiving therapy at 1.5 W/cm<sup>2</sup>. Both groups underwent passive stretching exercises immediately after treatment. All were assessed before

and at the end of the 15 session course. Outcome measures included the number of trigger points, pain intensity at rest, cervical lateral range of motion, pain intensity on movement and the Neck Pain Disability Scale (NPDS).

While both groups demonstrated significant improvement compared with baseline, the number of trigger points decreased more among those in the PH group ( $p=0.01$ ). Significant improvement in pain intensity at rest was noted in the PH group, but not in the US group ( $p=0.001$ ). Significant improvement was noted in the NPDI scores for the PH group ( $p=0.001$ ), but not for the US group.

**Conclusion:** This study of patients with myofascial pain syndrome found that phonophoresis, using EMLA cream, is effective, and is superior to ultrasound for reducing symptoms

Ustun, N., et al. Efficacy of EMLA Cream Phonophoresis Comparison with Ultrasound Therapy on Myofascial Pain Syndrome of the Trapezius: A Single Blind, Randomized, Clinical Study. *Rheumatol Int*. 2014, April; 34(4): 453-457.

### ATACEPT FOR MULTIPLE SCLEROSIS

B cells play a key role in the pathogenesis of several autoimmune diseases, including multiple sclerosis (MS). Atacept is a fully humanized, recombinant fusion protein which binds to cytokines involved in cell differentiation, maturation and survival. This study assessed the safety and efficacy of atacept for use in patients with relapsing MS.

This randomized, double-blind, controlled trial included patients 18 to 60 years of age with relapsing remitting MS. The subjects were randomized to receive atacept at 25, 75 or 150 mg or matching placebo. The medication was received twice per week for four weeks, and then once per week for 32 weeks. All patients underwent a standardized neurological examination, with assessments using the Expanded Disability Status Scale (EDSS). An MRI was completed at the screening, on study day one, week 12 and then every four weeks to week 36. The primary endpoint was the change in number of



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gadolinium enhancing lesions from weeks 12 to 36.

Of the patients screened, 255 were randomly assigned to the treatment group. During the double-blind portion of the trial, the proportion of patients remaining free of relapse was greater in the placebo group than in any treatment group. Patients with more than one relapse were exclusively in the ataccept groups. The number of gadolinium enhancing T-1 lesions per scan was similar in all groups. The study was discontinued by the safety monitoring board.

**Conclusion:** This study of patients with MS who were treated with a recombinant fusion protein that suppresses B cell function and antibody production was discontinued due to an unexpected increase in relapses.

Kappos, L., et al. Ataccept in Multiple Sclerosis (ATAMS): A Randomized, Placebo-Controlled, Double-Blind, Phase 2 Trial. *Lancet Neur.* 2014, April; 13: 353-363.

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