

# REHAB IN REVIEW

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## VITAMIN D AND IDIOPATHIC BENIGN PAROXYSMAL POSITIONAL VERTIGO

Benign paroxysmal positional vertigo (BPPV) is one of the most common vestibular disorders. The mechanism for BPPV is thought to be free floating otolith debris, or debris attached to the cupula. However, little data is available concerning the underlying cause of otoconial degeneration and detachment. As BPPV and osteoporosis have been associated, this study sought to determine whether vitamin D levels might also be associated with the development of BPPV.

A vestibular clinic recruited 100 consecutive patients, each with a diagnosis of idiopathic BPPV. These patients were compared with 192 community based controls without dizziness or imbalance. Vitamin D levels were compared between the groups.

Serum levels of 25 hydroxyvitamin D were lower in patients with BPPV than in controls ( $p=0.001$ ). This finding held true among both men and women. Multivariate regression analysis revealed that vitamin D insufficiency and deficiency were associated with BPPV with odds ratios of 3.8 and 23, respectively.

**Conclusion:** This study demonstrates an association between idiopathic benign paroxysmal positional vertigo and decreased serum vitamin D.

Jeong, S., et al. Decreased Serum Vitamin D and Idiopathic Benign Paroxysmal Positional Vertigo. *J Neurol.* 2012, October 25; DOI: 10.1007/500415-012-6712-2.

## STATIN USE AND CANCER RELATED MORTALITY

Statins have been found to inhibit the production of endogenous cholesterol and to block protein

preylation. As a reduction in the availability of cholesterol might lead to decreased proliferation and migration of cancer cells, this study reviewed the effect on cancer related mortality of statin use.

The Danish Registry of Medicinal Products Statistics records information concerning all prescribed drugs dispensed at a Danish pharmacy since 1995. Using data from this registry, daily doses for statin users were estimated. In addition, the authors identified patients who had been diagnosed with cancer between 1995 and 2007. Mortality data from the same population were reviewed, with causes of death determined. From these data, the relationship between cancer-related mortality and statin use was reviewed.

Among patients 40 years of age or older, 18,721 used statins regularly, while 277,204 had never used statins or any other cholesterol lowering drug. The cumulative incidence of death from any cause was lower among statin users than among patients who had never used these medications ( $p<0.001$ ). Among those with a diagnosis of cancer, the cumulative incidence of death from cancer was lower among statin users than among those who had never used statins ( $p<0.001$ ).

**Conclusion:** This study found that statin use in patients with cancer is associated with reduced cancer related mortality.

Nielsen, S., et al. Statin Use and Reduced Cancer-Related Mortality. *N Eng J Med.* 2012, November 8; 367 (19): 1792-1802.

## WEIGHT LOSS AND LOW BACK PAIN

Obesity has become pandemic in western society, with low back pain (LBP) common among those with morbid obesity. Despite the many

studies focusing on the interplay between obesity and LBP, many of the related mechanisms remain obscure. This study explored the effect of weight loss on quality-of-life and back pain among obese patients.

Thirty-five morbidly obese adults scheduled for bariatric surgery were enrolled in this study. Abdominal CT scans were obtained at the lumbar vertebral levels before and at one year after surgery. From these data, measurements of L-4 and L-5 intervertebral disc height were obtained. Axial and radicular pain levels were assessed with a Visual Analogue Scale. Quality of life was assessed before and one year after surgery with the Moorehead-Ardelt Quality of Life Questionnaire.

One year after surgery, the subjects' average weight had decreased from 119.6 kg to 82.9 kg ( $p<0.001$ ). Vertebral disc height had increased from six to eight mm ( $p<0.001$ ) and radicular pain had decreased markedly ( $p<0.001$ ). In addition, a significant improvement was noted on one of two quality-of-life scales. However, no significant relationship was found between the degree of weight reduction and the increments in disk space increase or back pain improvement.

**Conclusion:** This study of obese subjects undergoing bariatric surgery found a significant decrease in low back and radicular pain, as well as a marked increase in lumbar vertebral disc height, at one year after surgery.

Lidar, Z., et al. Intervertebral Disc Height Changes after Weight Reduction in Morbidly Obese Patients and its Effect on Quality-Of-Life and Radicular and Low Back Pain. *Spine.* 2012, Nov 1; 37(23): 1947-1952.

## VITAMIN D AND ORTHOSTATIC HYPOTENSION

Orthostatic hypotension is common among the elderly and is

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associated with falls, fractures and significant morbidity. Vitamin D supplementation has been found to reduce the risk of falls, although potential mechanisms of this effect remain unclear. This study assessed the effect of vitamin D on orthostatic hypotension.

This case control study included community dwelling individuals 64 years of age or older who were not receiving vitamin D supplements. Cases included subjects who were diagnosed with orthostatic hypotension, consecutively recruited between January and February of 2009. Controls were age and gender matched, and had no history of blackouts, falls or orthostatic dizziness in the previous year. Blood samples and clinical data were compared between the two groups.

Seventy-six subjects were included in this analysis, including 38 cases and 38 controls. Subjects with orthostatic hypotension had significantly lower serum 25 (OH) D levels than did controls (p=0.0002). In the combined group, an inverse association was found between serum 25 (OH) D and baseline diastolic blood pressure (p=0.03). While there was a trend toward higher systolic blood pressure among those with lower vitamin D levels, this finding did not reach statistical significance (p=0.08).

**Conclusion:** This study of elderly individuals found serum 25 (OH) D levels to be lower in subjects with orthostatic hypotension, with a significant association found between vitamin D levels and diastolic blood pressure.

McCarroll, K., et al. Vitamin D and Orthostatic Hypotension. **Age and Aging**. 2012; 41: 810-813.

**ANTICHOLINERGIC THERAPY VERSUS ONABOTULINUMTOXIN A FOR URGENCY URINARY INCONTINENCE**

Urgency urinary incontinence is a prevalent condition, affecting up to 19% of older women in the United States. The primary treatment for this condition is anticholinergic medication. Previous studies have demonstrated that onabotulinumtoxin A is effective in treating resistant urgency urinary incontinence, although direct comparisons with anticholinergic agents have been

lacking. This study compared the effects of an oral anticholinergic medication to a single injection of onabotulinumtoxin A for reducing episodes of urgency urinary incontinence.

This multi-center, randomized, double-blind, placebo-controlled trial involved women without neurologic disease, each with moderate to severe urgency urinary incontinence. The patients were randomized to receive either the oral anticholinergic drug solifenacin, at a dose of 5 mg per day for six months, combined with a single detrusor muscle injection of saline, or a placebo, combined with a single detrusor muscle injection of 100 units of onabotulinumtoxin A. At six months, all oral study medications were discontinued, with patients followed for an additional six months. The primary outcome measure was the change from baseline in the number of episodes of urgency urinary incontinence over six months.

A total of 241 patients had data available for the primary outcome analysis. The mean reduction in episodes of incontinence per day was similar between the two groups during months one through six (p=0.81). A complete resolution of incontinence was reported by 27% of the onabotulinumtoxin A group and 13% of the anticholinergic group (p=0.003).

**Conclusion:** This study of women with urgency urinary incontinence found no significant difference in episodes of incontinence or quality of life between groups treated with anticholinergic drugs and onabotulinumtoxin A.

Visco, A., et al. Anticholinergic Therapy versus Onabotulinumtoxin A for Urgency Urinary Incontinence. **N Eng J Med**. 2012, November 8; 367 (19): 1803-1813.

**STERIOD, PHONOPHORESIS FOR CARPAL TUNNEL SYNDROME**

Carpal tunnel syndrome (CTS) is thought to be due to entrapment of the median nerve in the carpal tunnel at the wrist. Conservative treatments for CTS include rest, splinting, nonsteroidal anti-inflammatory drugs (NSAIDs), oral or injected steroids, ultrasound and laser therapy. Studies of iontophoresis and phonophoresis as methods to deliver steroids have produced mixed findings. This study

was designed to compare the efficacy of iontophoresis and phonophoresis delivery of dexamethasone for patients with CTS.

This randomized trial included 34 right-handed patients with CTS, with symptoms of at least one month in duration. Of these, 18 patients had bilateral disease. The participants were randomized to receive either iontophoresis (group A) or phonophoresis (group B) delivery of dexamethasone sodium phosphate 0.4%. The medication was applied over the wrist for five minutes, five days per week, for two weeks. Outcome measures for each wrist consisted of a visual analogue scale of pain, pinch strength, hand grip strength and electrodiagnostic testing. Measurements were performed before and after treatment and again at four-week follow-up.

Measures of finger pinch and hand grip strength were significantly improved in both groups, with the mean changes higher among those treated in group B both at treatment end and at four-week follow-up ( $p=0.0002$  and  $p=0.008$  respectively). Electrodiagnostic studies revealed that motor distal latency decreased in both groups, with mean changes significantly greater in group B at both treatment end and four-week follow-up.

**Conclusion:** This study of patients with carpal tunnel syndrome demonstrates that delivery of dexamethasone through phonophoresis is more effective than delivery by iontophoresis in reducing pain and dysfunction associated with this syndrome.

Bakhtiyari, A., et al. Phonophoresis of Dexamethasone Sodium Phosphate May Manage Pain and Symptoms of Patients with Carpal Tunnel Syndrome. *Clin J Pain*. 2012 DOI: 10.1097/AJP.0b013e318255c090

### DEPRESSIVE SYMPTOMS AND PHYSICAL THERAPY

A number of studies have demonstrated that depression and chronic pain are common comorbid conditions. Those suffering from both conditions are likely to experience greater levels of disease related burden. This study was designed to review the trajectory of depressive symptoms among patients seeking

physical therapy for work related orthopedic injuries.

One hundred six patients with work-related musculoskeletal injuries and clinically significant depressive symptoms were included in this prospective study. The subjects underwent three physical therapy sessions per week over seven weeks of treatment, designed to reduce pain and disability. All completed self-report questionnaires evaluating pain intensity, depressive symptoms, pain catastrophizing, fear of movement and pain self-efficacy. Each patient was assessed for depression and pain at treatment onset, mid-treatment, treatment end and one year after treatment discharge.

Of the 235 patients with work-related musculoskeletal back or neck injuries, 124 met the criteria for initial levels of depressive symptoms. After therapy, the participants experienced a mean reduction in depressive symptoms of 27.4%. At the mid-treatment assessment, depressive symptoms resolved in 40.6% of the sample. This group was labeled as responders. At one year, the responders were significantly more likely to return to work ( $p=0.04$ ), with significantly lower pain levels at one year, than non-responders ( $p=0.03$ ).

**Conclusion:** This study demonstrates that resolution of depressive symptoms over the course of physical therapy is associated with long-term improvements in pain and disability after musculoskeletal injury.

Wideman, T., et al. Recovery from Depressive Symptoms over the Course of Physical Therapy: A Prospective Cohort Study of Individuals with Work-Related Orthopedic Injuries and Symptoms of Depression. *J Orthop Sports Phys Ther*. 2012; 42(11): 957-967.

### WORK AND HEADACHE

The worldwide point prevalence of headache has been estimated to be 46% in the general adult population. Disability attributed to headache is thought to be substantial. This study examined the contributions of occupational, psychological and mechanical factors to the onset and severity of headaches.

Subjects included employees from a wide variety of occupations in Norway, with baseline data gathered

from November of 2004 through May of 2008. Follow-up data were gathered from September of 2006 to May of 2010. A questionnaire was distributed in order to gather data concerning background, work organization, psychological and social factors at work, organizational change, attitudes towards work, personality, physical factors, tobacco abuse, alcohol use, mental health, mastery of work, working ability and health complaints. Included within these questionnaires were queries about headache frequency and intensity.

Of the psychological, social and mechanical factors tested, worse headache severity was found to be associated with higher quantitative demands of the job, higher role conflict, lower decision control, lower control over work intensity and lower job satisfaction. Job satisfaction was found to both influence and be influenced by headache pain.

**Conclusion:** This study suggests that headache frequency and severity are related to on-the-job conditions, including control over work environment and job satisfaction.

Christiansen, J., et al. Work and Headache: A Prospective Study of Psychological, Social, and Mechanical Predictors of Headache Severity. *Pain*. 2012, October; 153 (10): 2119-2132.

### COGNITIVE DYSFUNCTION AND PHYSICAL ACTIVITY AFTER STROKE

Stroke survivors, even those with only mild motor impairment, may have a more sedentary lifestyle after the stroke. In addition, cognitive impairment, which is common in stroke patients, has been found to be a predictor of reduced physical activity. This study was designed to better understand the relationships between pre-stroke cognitive impairment, cognition in the acute phase after stroke, and cognitive and physical impairment one year after stroke.

A total of 74 patients, all admitted to a geriatric stroke unit in Sweden, were included in the study. The patients were stratified into minor stroke and major stroke groups using the National Institutes of Health Stroke Scale (NIHSS). The level of disability and functional outcome

before stroke onset, on admission and discharge from the stroke unit and at one-year follow-up were assessed using the Modified Rankin Scale (MRS). Physical activity was determined by patient interview, with cognition assessed using the Cognitive Impairment Questionnaire (CIMP-QUEST). In addition, all patients were assessed with a neuropsychological test battery at hospital admission and at one-year follow-up.

Eighty percent of patients with pre-morbid global cognitive impairment demonstrated low physical activity, as compared with 33% of those without pre-morbid cognitive impairment ( $p=0.02$ ). Those with impaired cognition before stroke had an eight-fold greater risk of having low level physical activity one year after stroke, as compared with those with intact cognition ( $p=0.03$ ). Nearly all patients displayed cognitive impairment in the acute phase of stroke. Factors predicting a low level of physical activity one year after stroke included impaired global cognition before stroke, visual neglect and impaired logical deductive ability in the acute phase, and impaired global cognition, executive function and visual memory at one-year follow-up.

**Conclusion:** This study of elderly stroke survivors suggests that impaired cognition and executive function increase the risk for low levels of physical activity after a stroke.

Pahlman, U., et al. Cognitive Dysfunction and Physical Activity after Stroke: The Gothenburg Cognitive Stroke Study in the Elderly. *J Stroke Cerebrovasc Dis.* 2012, November; 21(8): 652-658.

### EFFECTS OF ANTINEUROPLASTIC DRUGS ON STROKE OUTCOME

A number of drug classes have been shown to inhibit neuroplasticity. These include anticholinergic agents, voltage sensitive sodium channel active anticonvulsants, GABA-ergic anticonvulsants, alpha-1 noradrenergic and alpha-2 adrenergic agonists and neuroleptics. However, relevant, prospective studies with human subjects have been limited. This study assessed the effects of antineuroplastic drugs on outcome in stroke rehabilitation.

Data were obtained from the Locomotor Experience Applied Post Stroke (LEAPS) trial of rehabilitation interventions for gait impairment after stroke. This study divided subjects into a task specific locomotor training program (LTP), applied either early or late, or a home exercise program (HEP). The authors identified 408 participants taking one or more antineuroplastic drugs. During the trial, the patients were assessed at two and 12 months for functional walking level, self-selected walking speed and impairments on measures of lower and upper extremity function and cognition. These outcomes were compared among patients using benzodiazepines, alpha 1 noradrenergic and alpha2 noradrenergic blockers and sodium channel anticonvulsants.

Data were included for 408 participants at an average of 63.8 days post-stroke. While results revealed associations among several major classes of drugs, and lesser gains in functional walking, these differences did not reach statistical significance when corrected for multiple comparisons. The largest amount of variance was noted with voltage sensitive sodium channel anticonvulsants and their effect on functional walking level, although this effect was small. The association between drug classes and reduced success seemed most related to differences in impairment in abilities among those for whom the drugs were prescribed.

**Conclusion:** This study of patients with acute stroke did not demonstrate any significant deleterious effects of several antineuroplastic drugs on the stroke rehabilitation process.

Nadeau, S., et al. A Prospective Test of the Late Effects of Potentially Antineuroplastic Drugs in a Stroke Rehabilitation Study. *Int J Stroke.* 2012, DOI: 10.1111/j.1747-4949.2012.00920

### BIOMECHANICAL MECHANISMS FOR CHRONIC DISCOGENIC BACK PAIN

Closely linked to discogenic back pain are annulus fissures and the ingrowth of nerves and blood vessels. As fluid pressure normally extends from the nucleus into the inner and middle annulus, it would be expected

to collapse any blood vessel. Reduced pressure within a fissure could, therefore, provide a route for ingrowth of blood vessels and nerves. In addition, proteoglycans have been shown to inhibit the growth of nerves. Any loss of proteoglycans from within an annulus fissure may therefore increase their attractiveness to ingrowing vessels and nerves. This study was designed to better understand whether fissures in the annulus of degenerated human discs are conducive to the ingrowth of nerves and blood vessels.

Cadaveric and surgically removed discs were used to perform three complementary studies. First, cadaveric discs containing annulus fissures were subjected to compression, with stresses measured throughout the disc. Second, 25 surgically removed discs were examined histologically. Safranin O was used to stain proteoglycans to measure their loss. Third, using 21 cadaver discs from four individuals, the proteoglycans and water concentrations in regions containing annulus fissures were compared, with the same results obtained from intact regions within the discs.

The results revealed that compressive stress was reduced by an average 36% to 46% within the fissures. Proteoglycans were focally depleted within the fissures, typically by 40% at a distance 600  $\mu\text{m}$  from the fissure axis. Physically disrupted regions of annulus, which included fissures, lost 36% to 54% of their proteoglycans, as compared with adjacent intact regions of annulus.

**Conclusion:** This study suggests that annulus fissures form a protective low-pressure microenvironment, with decreased proteoglycan concentration providing an environment conducive to the ingrowth of nerves and blood vessels.

Stefanakis, M., et al. Annulus Fissures Are Mechanically and Chemically Conducive to the Ingrowth of Nerves and Blood Vessels. *Spine.* 2012, October 15; 37(22): 1883-1891.

### COGNITIVE BEHAVIORAL THERAPY FOR DEPRESSION IN THE ELDERLY

Depression is a prevalent diagnosis in the elderly population, with major depressive disorders affecting up to 9.4% of community

dwelling older people. This meta-analysis was designed to better understand the benefit of cognitive behavioral therapy (CBT) for depression in older patients.

The authors conducted a literature review, searching for randomized, controlled trials involving CBT for depression in the elderly. Patients were 50 years of age or older, with CBT compared to an active or a non-active control condition. Evidence-based depression outcome measures were used in all studies. Of the 485 studies identified, 23 were included in the meta-analysis and meta-regression.

Overall, participants who received CBT had significantly greater odds of remitting or of enjoying clinically significant improvement than did non-active controls. This pattern held true at six months, but not at later time periods. However, participants who received CBT did not have significantly greater odds of remitting than did those who received other treatments.

**Conclusion:** This meta-analysis of randomized controlled trials suggests that cognitive behavioral therapy for depression in older people is more effective than treatment as usual. However, this treatment was not found to be superior to other treatments.

Gould, R., et al. Cognitive Behavioral Therapy for Depression in Older People: A Meta-Analysis and Meta-Regression of Randomized Controlled Trials. *JAGS*. 2012, October; 60(10): 1817-1830.

### **LOW MOLECULAR WEIGHT HEPARIN AND POST STROKE NEUROLOGIC DETERIORATION**

Patients with large artery occlusive disease are at high risk for early neurologic deterioration (END). For these patients, aspirin has limited prophylactic benefits. In the International Stroke Trial Study, unfractionated heparin reduced ischemic stroke recurrence during the period of treatment. The efficacy of low molecular weight heparin for preventing END has not yet been well studied. This study was designed to further investigate this relationship.

This prospective, multicenter, randomized clinical trial included patients diagnosed as having acute ischemic stroke with large artery

occlusive disease. The participants were randomized to receive either nadroparin calcium 3,800 antifactor Xa IU/0.4 mL, subcutaneously twice-daily ( LMWH group) or aspirin at 160 mg once daily (aspirin group), within 48 hours of stroke onset for 10 days. All patients then received aspirin at 80 to 300 mg once daily for six months.

All subjects underwent a CT scan before randomization and again at day 10. Vascular imaging was performed to identify vascular stenosis, with vascular evaluation performed before or within three days of randomization. Baseline data included demographics, medical history and pre-stroke modified Rankin scale and NIHSS scores. The primary outcome event was END, defined as an increase of four points or more on the NIHSS, at 10 days from baseline, or by death as a result of a stroke.

A total of 353 patients were studied. Among those, END occurred within the first 10 days in 6.7% of the LMWH group and 13.9% of the aspirin group (p=0.03). Treatment with LMWH was associated with a lower frequency of stroke progression within the first 10 days (p=0.01). END was associated with six-month disability in both the LMWH and aspirin groups.

**Conclusion:** This study of patients with large artery occlusive disease and ischemic stroke found low molecular weight heparin to be superior to aspirin for the prevention of early neurologic deterioration and stroke progression within the first 10 days.

Wang, Q. Low Molecular Weight Heparin and Early Neurologic Deterioration in Acute Stroke Caused by Large Artery Occlusive Disease. *Arch Neurol*. 2012, November; 69 (11): 1454-1460.

### **DAY OF HOSPITALIZATION AND QUALITY OF STROKE CARE**

Previous studies from a range of countries have identified higher mortality in patients admitted to a hospital on weekends. Studies concerning stroke care have produced conflicting results. This study was designed to further determine whether the quality and safety of stroke care are affected by

whether a patient is admitted during the weekend.

The authors performed a literature review to identify indicators of quality stroke care, producing six indicators. These included brain scans on the day of admission, thrombolysis treatment, diagnosis of aspiration pneumonia in the hospital, seven-day in-hospital mortality, discharge to usual place of residence within 56 days and 30-day emergency readmission. The details of stroke admissions between April 2009 and March 2010 were extracted from the hospital episode statistics database. Outcomes were compared between those admitted on weekends and those admitted on weekdays.

Across the English hospital system, 93,621 stroke admissions were identified. Of those, 9.3% died in a hospital within seven days of admission and 17.1% died within 30 days. When comparing those admitted on the weekend to those admitted on the weekday, significant associations were found in all indicators except readmissions, with lower levels of treatment and worse outcomes in the weekend group. Seven day in-hospital mortality was nine percent in the weekday group and 10.3% in the weekend group (p<0.001). Discharge to the patient's usual place of residence occurred in 72.9% of the weekday group and in 71.3% of the weekend group (p<0.001). Aspiration pneumonia occurred in 5.1% of the weekday group and in 5.6% of the weekend group (p=0.003).

**Conclusion:** This large study of consecutive patients admitted for stroke in England found that those admitted on weekends had lower rates of receiving urgent treatments and experienced worse outcomes than did those admitted on weekdays.

Palmer, W., et al. Dying for the Weekend. A Retrospective Cohort Study on the Association between Day of Hospital Presentation and the Quality and Safety of Stroke Care. *Arch Neurol*. 2012, October; 69(10): 1296-1302.

### **ASPIRIN TO PREVENT RECURRENT VENOUS THROMBOEMBOLISM**

Patients with a first episode of unprovoked venous thromboembolism (VTE) are at a higher risk

for recurrence after anticoagulant therapy is discontinued. Long-term treatment with warfarin can reduce the recurrence of VTE, but this treatment has not been found to improve survival, and is associated with side effects. This study was designed to evaluate the efficacy of low dose aspirin in preventing the recurrence of VTE.

The Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) study was a double-blind, randomized, placebo-controlled trial involving patients with first ever unprovoked VTE. The subjects had completed anticoagulation therapy and were randomized to receive aspirin at 100 mg daily or a placebo. All patients attended follow-up visits at one and six months after randomization, and every six months thereafter, and were contacted by telephone or e-mail at the three-month mark between visits. All were instructed to report symptoms suggestive of a recurrence of VTE, bleeding or adverse effects of the medication, or any other clinically significant changes. Information for each patient was included for a period of up to four years after enrollment. The primary outcome measure was a recurrence of VTE, defined as objectively confirmed deep vein thrombosis, nonfatal pulmonary embolism or fatal pulmonary embolism.

During the follow-up period, a recurrent VTE occurred in 18% of the placebo group and in 14% of the aspirin group, at a rate of 6.5% per year versus 4.8% per year ( $p=0.09$ ). After adjusting for baseline characteristics, the hazard ratio with aspirin use was found to be 0.72 ( $p=0.06$ ). Occurrences during the period in which the subjects were receiving the study intervention were 7.6% per year with placebo and 4.8% per year with aspirin ( $p=0.03$ ). The risk of recurrence was higher during the first year of follow-up than in subsequent years. The secondary outcome of major vascular events occurred more frequently in the placebo group ( $p=0.01$ ). Clinically relevant bleeding occurred in eight patients in the placebo group and in 14 in the aspirin group.

**Conclusion:** This study of patients with a history of venous thromboembolism found that aspirin, at 100 mg daily, may be beneficial in preventing recurrent venous

thromboembolism and major vascular events.

Brighton, T., et al. Low Dose Aspirin for Preventing Recurrent Venous Thromboembolism. *N Eng J Med*. 2012, Nov 22; 367(21): 1979-1987

### IBUPROFEN AND EXERCISE-INDUCED INTESTINAL INJURY

The reported prevalence of nonsteroidal anti-inflammatory drug (NSAID) use among athletes varies widely among sports, ranging from 12% in cyclists to more than 90% in professional soccer players. Of the side effects of NSAIDs, gastrointestinal complications such as mucosal ulceration, bleeding, perforation and strictures have been noted. As exhaustive physical activity is thought to lead to small intestine injury, this study reviewed the effects of NSAID use on exercise-induced small intestinal injury in healthy athletes.

Nine healthy male cyclists or triathletes were included in the study. All spent three to 10 hours per week performing endurance sports. The volunteers had no abdominal complaints during daily activities, and had taken no medication for a least one month. Each was assessed for maximal workload capacity using a stationary cycle ergometer. The subjects were then tested in random order in four different situations; during and after cycling after intake of ibuprofen, during and after cycling without ibuprofen, rest after intake of ibuprofen, and rest without intake of ibuprofen. All subjects started cycling at a workload of 150 W after collection of baseline blood and urine. To assess small intestinal injury, plasma intestinal fatty acid binding protein levels (I-FABP) were determined. To assess small intestine permeability, urinary excretion of orally ingested multi-sugar test probes was completed.

Plasma I-FABP levels gradually increased during cycling, with ibuprofen intake resulting in even higher levels ( $p<0.0001$ ). The peak levels were significantly higher among those cycling with, compared to those cycling without, ibuprofen ( $p<0.05$ ). Ibuprofen consumption also increased these levels during rest ( $p=0.0003$ ). Small intestinal permeability increased, especially among those cycling with ibuprofen,

with levels reflecting a loss of gut barrier integrity.

**Conclusion:** This small study suggests that ibuprofen aggravates exercise-induced small intestinal injury and induces gut barrier dysfunction in healthy individuals.

Van Wijck, K et al. Aggravation of Exercise-Induced Intestinal Injury by Ibuprofen in Athletes. *Med Sci Sports Exerc*. 2012, December; 44 (12): 2257-2262.

### OUTCOME AFTER SEQUENTIAL HIP FRACTURE IN THE ELDERLY

Patients who sustain a single fragility fracture are at increased risk of sustaining additional fractures. This study was designed to report on the incidence, epidemiology and outcomes of sequential fractures.

Data were abstracted from the Scottish Hip Fracture Audit, which is a collection of data from the 22 Scottish hospitals which treat patients for hip fractures. Each patient's second fracture and survival status was analyzed at six-month intervals for up to eight years from the time of the initial injury. More detailed analysis was performed using 120-day intervals for up to two years to identify any patterns in the period after the initial injury.

Of the 20,267 patients who initially presented with unilateral fractures, 32% died within the first 12 months. Of those who survived, 2.5% sustained a second fracture. The risk of sequential fracture was highest in the first twelve months, affecting three percent of surviving patients and decreasing to two percent per survival year thereafter. Female gender and greater age were significantly associated with a second fracture ( $p=0.001$  and  $p=0.005$ , respectively).

Age and ability to walk unaided in an institutional setting were the strongest predictors of falls. Patients able to walk without assistive devices in their homes were least likely to sustain another fracture. Of those with a second fracture, 63% survived for up to 12 months. Among those with a second fracture within four months of the initial injury, six percent were walking unassisted and 32% were living at home by 120 days post-injury.

**Conclusion:** This study found that patients who sustain a second

fracture have less favorable outcomes than do those who have had only a single fracture.

Hott, G., et al. Outcomes after Sequential Hip Fractures in the Elderly. **J Bone Joint Surg (Am)**. 2012, October 3; 94(19): 1801-1808.

### EARLY REHABILITATION AFTER LUMBAR SPINE FUSION

In the past two decades, the number of spinal fusion procedures has risen dramatically throughout the world. Nevertheless, few studies have reviewed different rehabilitation strategies after these procedures. This study was designed to determine whether early initiation of rehabilitation improves outcomes.

This randomized, controlled trial included patients planning an instrumented lumbar spinal fusion due to degenerative disc disease or spondylolisthesis. The patients were randomized to receive rehabilitation beginning at either six or 12 weeks after surgery. Both groups followed the same rehabilitation program. The therapy consisted of four, two-hour sessions, including both physical and occupational therapies. The primary outcome measure was the Oswestry Disability Index (ODI), with secondary outcomes including the Dallas Pain Questionnaire, the Low Back Pain Rating Scale and days of sick leave taken after surgery.

At the six-month follow-up, ODI scores were reduced by six points in the six-week group and by 15 points in the twelve-week group ( $p < 0.05$ ). At the one-year follow-up, the six-week group had obtained a reduction of five points, and the 12 week group a reduction of 20 points, on the ODI ( $p < 0.01$ ). For back pain at six months the six-week group demonstrated a median reduction of 2.2 points and the 12 week group a median reduction of 3.3 points ( $p < 0.05$ ), with similar differences found at 12-month follow-up ( $p = 0.01$ ).

**Conclusion:** This study of patients undergoing lumbar spine fusion found better outcomes among those initiating rehabilitation at 12 weeks, as compared with six weeks, postoperatively.

Oestergaard, L., et al. The Effect of Early Initiation of Rehabilitation after Lumbar Spinal Fusion: A

Randomized Clinical Study. **Spine**. 2012, Oct 15; 37(21):1803-1809.

### FINGOLIMOD THERAPY FOR MULTIPLE SCLEROSIS

Fingolimod is the first of a new class of therapeutic compounds referred to as sphingosine 1-phosphate receptor modulators, recently approved for the treatment of multiple sclerosis (MS). This medication retains circulating lymphocytes in the lymph nodes, reducing central nervous system infiltration. This study was designed to better evaluate the effect of treatment with fingolimod for the treatment of MS.

This phase three clinical trial involved subjects 18 to 55 years of age with a diagnosis of MS, with a relapsing remitting course. The patients were randomized to receive daily doses of fingolimod at 0.5 mg or 1.25 mg, or a matching placebo, for two years. Treatment efficacy was measured by MRI at zero, six, 12 and 24 months.

A total of 1,033 patients completed the study, with 945 patients completing the full two years. Treatment with fingolimod resulted in rapid, sustained reductions in inflammatory lesion activity at six, 12 and 24 months ( $p < 0.001$ ). A greater reduction in disease burden was noted in the treatment group, as compared with the placebo group ( $p < 0.05$ ). Fingolimod significantly reduced brain volume losses as early as six months, demonstrating sustained reductions for up to 24 months ( $p < 0.001$ ).

**Conclusion:** This study of patients with relapsing remitting multiple sclerosis found that fingolimod can reduce the rate of relapse, progression of disability and progression of brain atrophy

Radue, E., et al. Impact of Fingolimod Therapy on Magnetic Resonance Imaging Outcomes in Patients with Multiple Sclerosis. **Arch Neurol**. 2012, October; 2012; 69(10): 1259-1269.

### GABAPENTIN FOR REFRACTORY CHRONIC COUGH

Chronic cough is a common clinical symptom for up to 16% of the population. Refractory cough shares similarities with other disorders

associated with central sensitization, such as neuropathic pain. As the neuromodulator, gabapentin has been found to be effective for treating pain with central sensitization, this study was designed to test whether gabapentin may be an effective treatment for patients with refractory chronic cough.

This randomized, placebo-controlled, double-blind study included 65 patients diagnosed with refractory chronic cough. All patients had failed to respond adequately to several treatment trials before study entry. The subjects were randomized to receive either gabapentin or a placebo. All followed a six-day dose escalation schedule, until they reached a maximum of 1,800 mg per day. All participants kept a cough diary. The primary outcome measure was the change in cough specific quality-of-life, as measured from baseline to eight weeks of treatment.

A reduction in cough frequency during the treatment period was significantly greater in the treatment group than in the placebo group ( $p = 0.046$ ). Patients in the treatment group were found to have greater improvements in cough specific quality-of-life scores than the placebo group ( $p = 0.04$ ).

**Conclusion:** This study of patients with chronic cough found that gabapentin may be an effective treatment for this disorder.

Ryan, N., et al. Gabapentin for Refractory Chronic Cough: A Randomized, Double-Blind, Placebo-Controlled Trial. **Lancet**. 2012, November 3; 380(9853): 1583-1589.

### HETEROTOPIC OSSIFICATION IN SPINAL CORD INJURY

Heterotopic ossification (HO) is commonly seen in patients with spinal cord injuries (SCIs), although the exact mechanism remains unknown. This study was designed to help clarify risk factors for the development of HO in patients with SCI.

This case controlled study included patients identified at a level I trauma center, all of whom were treated for SCI between 2002 and 2010. From that database, 132 patients with HO were compared to 132 patients without HO. All were followed for 125 days and were screened for HO by verbal query and

(Continued from page 2)

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physical examination. Ultrasound was performed every two weeks, with those with positive findings undergoing CT or MRI to confirm the diagnosis.

Patients with complete SCIs had a six-fold increased risk of developing HO. A two-fold increased risk of HO development was found in patients with associated thoracic trauma. Other factors associated with an increased risk of HO included tobacco abuse, associated spasticity, urinary tract infection, pneumonia and the presence of tracheostomy. Several factors which had been identified in previous studies as risk factors were not identified in this study, including gender, age, length of hospitalization or ICU stay, presence of pressure sores, and deep venous thrombosis.

**Conclusion:** This study of patients with spinal cord injury found that the risk of developing heterotopic ossification is higher among those with spasticity, thoracic trauma, tobacco abuse, pneumonia, the presence of tracheostomy and urinary tract infections.

Mustafa, C., et al. Risk Factors for Heterotopic Ossification in Patients with Spinal Cord Injury: A Case-Control Study of 264 Patients. *Spine*. 2012, November 1; 37(23): 1953-1957.

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