

# REHAB IN REVIEW

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## CLAZOSENTAN FOR VASOSPASM AFTER SUBARACHNOID HEMORRHAGE

Vasospasm contributes to delayed ischemic neurologic deficits (DIND), occurring in up to 40% of cases of aneurysmal subarachnoid hemorrhage (aSAH). Clazosentan is a selective endothelial receptor antagonist which, in previous studies, has resulted in a dose-dependent reduction in moderate or severe angiographic vasospasms. This phase 3 study investigated the utility of clazosentan for reducing vasospasm related morbidity and mortality in patients with aSAH.

This prospective, multicenter, international, randomized, double-blind, placebo-controlled trial included patients 18 to 75 years of age with an aSAH caused by a ruptured saccular aneurysm, secured by endovascular coiling. After coiling, the patients were randomized to receive intravenous clazosentan at five or 15 mg/h, or a placebo for up to 14 days. Before coiling, all subjects underwent a CT scan and digital subtraction angiography or CT angiography. Additional CT scans were performed 12 to 48 hours after the coiling procedure, at discharge, at six weeks after hemorrhage and in cases of worsening neurologic condition. Neurologic assessments were performed every six hours after treatment until day 14, using the modified Glasgow Coma Scale and the abbreviated National Institutes of Health Stroke Scale. The Glasgow Outcome Scale - Extended Version (GOSE) and the modified Rankin Scale were utilized at week 12. The primary efficacy endpoint was vasospasm related morbidity and all cause mortality within six weeks post-SAH. The main secondary endpoint was the GOSE score, characterized as good (>4) or poor (≤4).

Vasospasm related morbidity and all-cause mortality occurred in 27% of the placebo group, 24% of the clazosentan 5 mg/h group and 15%

of the clazosentan 15 mg/h group. A significant improvement was seen in the clazosentan 15 mg/h treatment group ( $p=0.007$ ), but not in the clazosentan 5 mg/h group. DIND was significantly reduced with clazosentan 15 mg/h (10%) as compared with placebo (21%). Rates of vasospasm-related new cerebral infarctions were 13%, 16%, and 7% with placebo, clazosentan 5 mg/h, and clazosentan 15 mg/h, respectively. Poor functional outcome occurred in 24% in the placebo group, compared with 25% in the clazosentan 5 mg/h group and 28% in the clazosentan 15 mg/h group, respectively.

**Conclusion:** This study of the endothelial receptor antagonist clazosentan found that this drug at 15 mg/h could significantly reduced post aSAH vasospasm related morbidity and all cause mortality. This drug did not however significantly improve Glasgow Outcome Scale scores

Macdonald, R., et al. Randomized Trial of Clazosentan in Patients with Aneurysmal Subarachnoid Hemorrhage Undergoing Endovascular Coiling. *Stroke*. 2012, June; 43 (6): 1463-1469.

## GALANTAMINE FOR POST-STROKE APHASIA

Linguistic restoration is important for the well-being and independence of the stroke survivor. Several studies have reported that cholinergic boosting may beneficially impact stroke patients with aphasia. This study investigated changes in linguistic function in chronic, post-stroke aphasia by augmenting cholinergic neurotransmission using galantamine, a reversible and competitive acetylcholinesterase inhibitor.

This prospective, open label study included patients with a history of ischemic stroke, suffering from chronic aphasia at a minimum of one year after stroke onset. The patients

were randomly assigned to a control group or a treatment group, with the latter receiving 8mg/day of galantamine for four weeks, followed by 16 mg/day for 12 weeks. All participants underwent diagnostic studies, including blood tests, cardiac workup and neuropsychological assessment. Linguistic function was evaluated by the Aphasia Quotient (AQ) of the Western Aphasia Battery (WAB)

A total of 45 patients were randomized in this trial. At follow-up, significant improvement in AQ scores was seen in the treatment group ( $p=0.007$ ), but not in the control group ( $p=0.308$ ). Detailed analysis revealed significant improvements in the spontaneous speech, comprehension and naming domains ( $p=0.027$ ,  $p=0.018$  and  $p=0.013$ , respectively).

**Conclusion:** This study suggests that the administration of galantamine may facilitate linguistic progression among patients with chronic post-stroke aphasia.

Hong, J., et al. Galantamine Administration and Chronic Post-Stroke Aphasia. *J Neurol Neurosurg Psychiatry*. 2012, July; 83(7): 675-680.

## AMANTADINE FOR SPORTS RELATED CONCUSSIONS

For those who sustained a mild traumatic brain injury (TBI), clinical manifestations may include physical, cognitive, emotional or sleep-related disturbances. Several animal studies have demonstrated that medications that improve dopamine transmission lead to improvements in functional outcomes. This study was designed to determine whether amantadine, a medication that presynaptically facilitates the release of dopamine and inhibits reuptake, may be of benefit to patients with a concussion.

This retrospective study included 25 adolescents treated at a university sports medicine concussion program,

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all of whom had failed to recover within 21 days of the concussion. The patients received 100 mg of amantadine twice per day for three to four weeks. The control group had been treated conservatively at the same clinical concussion program, before the introduction of the amantadine treatment protocol. All participants completed an Immediate Post-concussion Assessment and Cognitive Test (ImPACT) at baseline and again at 40 to 50 days post-injury. Symptoms were reviewed at those time intervals.

At follow-up, symptoms in both groups had improved. However, the amantadine group demonstrated fewer symptoms ( $p=0.005$ ), more improved verbal memory ( $p=0.009$ ), and faster reaction times ( $p=0.05$ ) than did the control group.

**Conclusion:** This study of adolescent athletes demonstrates that amantadine, taken 100 mg twice per day, may reduce symptoms and improved verbal and reaction time performances to a greater extent than does conservative treatment alone.

Reddy, C., et al. Efficacy of Amantadine Treatment on Symptoms and Neurocognitive Performance among Athletes following Sports Related Concussion. **J Head Trauma Rehabil.** 2012; DOI: 10.1097/HTR.Obo12e318257fbc6

### **EXERCISE MODERATES EFFECTS OF APOE**

The presence of an APOE  $\epsilon 4$  allele is an established genetic risk factor for Alzheimer disease (AD). It is also known that cognitively normal adults with an APOE  $\epsilon 4$  allele show greater cortical amyloid deposition. As physical exercise has been shown to be protective against cognitive decline, this study was designed to assess whether exercise may affect amyloid deposition in patients with the APOE  $\epsilon 4$  allele.

Subjects included cognitively normal adults, with a subset including adult children of parents diagnosed with AD. All underwent APOE genotyping. Clinical assessments were completed to determine history of diabetes mellitus, hypertension, neurological illness, depression or cardiovascular compromise. Subjects also completed a questionnaire to determine their history of walking, running and jogging for the previous 10 years.

Cerebrospinal fluid samples were taken from 165 subjects and analyzed for A $\beta$ 42 level. Amyloid imaging was performed for 163 subjects. The binding potential values from four regions of interest were averaged to calculate a mean cortical binding potential (MCBP). The MCBP value has been found to correlate inversely with CSF A $\beta$ 42 level and to predict progression from cognitively normal status to symptomatic AD.

A regression model revealed significant exercise group ( $p<0.001$ ) and APOE status ( $p<0.001$ ) differences. High exercise individuals had lower MCBP than did low exercise individuals, and APOE  $\epsilon 4$  positive individuals had higher MCBP than did APOE  $\epsilon 4$  negative individuals. There was an exercise group by APOE interaction, demonstrating a greater effect of exercise upon those who were APOE  $\epsilon 4$  positive than upon those who were APOE  $\epsilon 4$  negative ( $p=0.02$ ).

**Conclusion:** This study of cognitively normal individuals suggests that those who are positive for the APOE  $\epsilon 4$  allele are at greater risk for amyloid deposition, and that this problem can be mitigated by increasing levels of exercise.

Head, D., et al. Exercise Engagement as a Moderator of the Effects of APOE Genotype on Amyloid Deposition. **Arch Neurol.** 2012, May; 69(5): 636-643.

### **STATINS AND HEMORRHAGIC STROKE**

A number of studies have indicated that HMG-CoA reductase inhibitors (statins) may be neuroprotective after stroke, including intracerebral hemorrhage (ICH). However, relevant data from human studies have been somewhat conflicting. This study was designed to review the relationship between statin use and ICH outcome.

This prospective study enrolled consecutive patients presenting to 11 participating hospitals in Ontario, Canada, with a diagnosis of ischemic stroke, intracranial hemorrhage or transient ischemic attack. Consecutive patients with confirmed intracranial hemorrhage were isolated as potential subjects for this study. Data were abstracted from the medical record included demographic history and data concerning hospital

mortality and functional outcome. Data were recorded concerning the preadmission use of statins. The primary outcome was the severity of stroke at presentation, as measured with the Canadian Neurological Scale, modified Rankin scale results at discharge, as well as 30-day and six-month mortality.

Between 2003 and 2008, data from 2,466 unique intracranial hemorrhage admissions were available for analysis. Statin users before stroke were less likely to have a severe stroke at presentation ( $p=0.0003$ ). However, no significant difference was seen between statin users and non-users in the likelihood of a poor discharge outcome ( $p=0.16$ ), 30-day mortality ( $p=0.36$ ) or six-month mortality ( $p=0.62$ ). Of those whose statins were discontinued during hospitalization, increased mortality was noted as compared to those whose medication was continued.

**Conclusion:** This study of patients hospitalized with an intracranial hemorrhage found that those taking statins prior to hospitalization have lower stroke severity at presentation. Discontinuing this medication after admission was found to be associated with a worse outcome.

Dowlatshahi, D., et al. Association of Statins and Statin Discontinuation with Poor Outcome and Survival after Intracerebral Hemorrhage. *Stroke*. 2012, June; 43 (6): 1518-1523.

#### **A NEW TEST FOR DIAGNOSING CUBITAL TUNNEL SYNDROME**

Cubital tunnel syndrome is the second most common peripheral entrapment neuropathy of the upper extremity. This disorder is thought to be related to repetitive or prolonged elbow flexion. The elbow flexion test is the most commonly used provocative test for diagnosing this syndrome. This study assessed the diagnostic utility of a test including shoulder internal rotation, abduction and flexion, combined with elbow flexion (SIREFT).

Subjects included 52 patients diagnosed with cubital tunnel syndrome and 123 controls. All of the subjects were evaluated with the elbow flexion test (EFT), the shoulder internal rotation test (SIRT) and the SIREFT. The SIREFT test was considered positive if symptoms of

the cubital tunnel syndrome developed within five seconds.

The sensitivity/specificity of the EFT, the SIRT and the SIREFT were 25%/100%, 58%/100% and 87%/98%, respectively. The sensitivity of the SIREFT was significantly better than that of the other two tests ( $p<0.001$ ). Of those undergoing electrodiagnostic studies, sensory nerve conduction of the ulnar nerve was influenced by the SIREFT position in 80% of the cases. None of the ulnar nerves of the control patients were influenced by this test.

**Conclusion:** This study demonstrates that the five second shoulder internal rotation elbow flexion test is a quick and easy provocative test for diagnosing cubital tunnel syndrome.

Kensuke, O., et al. Shoulder Internal Rotation Elbow Flexion Test for Diagnosing Cubital Tunnel Syndrome. *J Shoulder Elbow Surg*. 2012, June; 21(6): 777-781

#### **PAIN COPING SKILLS TRAINING AND WEIGHT MANAGEMENT FOR KNEE OSTEOARTHRITIS**

Overweight is associated with a four to five fold increased risk of knee osteoarthritis (OA). However, the pain of OA can interfere with successful weight loss behaviors. This study compared the long-term effects of a combined program involving pain coping skills training (PCST) and behavior weight management (BWM) strategies for overweight patients with painful knee OA.

This randomized, controlled study included 232 patients with a clinical diagnosis of OA. The subjects were randomized to receive six months of treatment in one of four programs: standard care (control), behavior weight management (BWM), patient coping skills training (PCST) or combined BWM and PCST. PCST was delivered for 24 weeks, with 12, weekly, 60-minute sessions for the first 12 weeks, followed by 12, 60-minute group sessions held every other week. This interaction was designed to decrease maladaptive pain catastrophizing, and increase adaptive coping strategies. BWM involved 60-minute group sessions held weekly for the first 12 weeks, with additional, 90-minute, supervised exercise sessions held three times per week for the first 12 weeks. During the last 12 weeks, 60-minute

group sessions were held every other week, with no supervised exercise sessions. The patients were assessed at baseline, post-treatment and at six and 12 months after the completion of treatment. All were assessed for pain, physical disability, psychological disability, gait velocity, pain catastrophizing, self-efficacy for arthritis and weight control.

Patients in the combined group showed significantly better long-term weight loss, as measured at two years, and significantly better outcomes in pain, physical disability, and psychological disability. Those in the combined group lost, on average, five percent of their weight, and were able to maintain, on average, 50% of this loss over two years.

**Conclusion:** This study of patients with knee osteoarthritis demonstrates that combining pain coping skills and weight management can assist with long-term weight reduction, as well as with reductions in pain and physical and psychological disability.

Somers, T., et al. Pain Coping Skills Training and Lifestyle Behavioral Weight Management in Patients with Knee Osteoarthritis: A Randomized, Controlled Study. *Pain*. 2012, June; 153(6): 1199-1209.

#### **RADIAL SHOCKWAVE THERAPY FOR CHRONIC PATELLAR TENDINOPATHY**

Patellar tendinopathy is a relatively common injury among athletes involved in jumping sports. A number of nonoperative treatments are available, although reports concerning the efficacy of these interventions are varied. As previous studies have demonstrated that shock wave therapy (SWT) can be effective for the management of tendinopathies, this study was designed to determine whether low energy SWT can be effective for the management of chronic patellar tendinopathy.

This retrospective study included 33 patients with chronic patellar tendinopathy who had undergone shockwave therapy between March of 2008 and April of 2009. These patients were compared with 33 others who had been treated with alternative conservative strategies. Those in the SWT group underwent a single session consisting of 10 shocks per second, with a total

energy flux density per session of 360 mJ/mm.

After the procedure, the patients were allowed immediate weight-bearing. Within one week of the procedure, all participants were allowed soft jogging activities as tolerated, with the time to return to competitive sports determined on a case-by-case basis. The primary outcome measures were a visual analogue scale score, the Victorian Institute of Sport Assessment (VISA) score and the Roles and Maudsley score, completed before treatment and at one, three and 12 months post-treatment.

Both groups improved on the VAS, with significantly greater improvement in the SWT group ( $p < 0.001$ ). Only the SWT group improved in VISA scores at each time point ( $p < 0.001$ ). The percentage of patients with excellent or good results on the Roles and Maudsley measure at one, three and 12 months after treatment was greater in the SWT group ( $p < 0.001$  for each comparison).

**Conclusion:** This study of patients with chronic patellar tendinopathy found that one session of shock wave therapy can reduce pain and increase function.

Furia, J., et al. A Single Application of Low Energy Radial Extracorporeal Shockwave Therapy is Effective for the Management of Chronic Tendinopathy. **Knee Surg Sports Traumatol Arthrosc.** 2012, DOI: 10.1007/s00167-012-2057-8

### DRIVING AFTER SEVERE TRAUMATIC BRAIN INJURY

After a traumatic brain injury (TBI), a significant focus of rehabilitation is to regain autonomy, which often includes the ability to drive. As safe driving requires multiple cognitive abilities, injuries to the brain are thought to reduce the capacity of some to return to safe driving. The predictive factors for this safe return in the severe TBI population have yet to be defined. This study investigated the road traffic accident rates before and after a severe TBI.

This study included patients with a severe TBI who were at least 16 years of age. The sample included 60 participants with a mean interval from injury of 4.25 years. Group A included all participants with a severe TBI who had been driving before the injury.

Within group B, group B1 comprised 22 participants who had driven before TBI and had resumed driving after rehabilitation. Group B2 comprised eight participants who had started driving after rehabilitation as they had been under age at the time of the injury.

All participants were evaluated with the Glasgow Outcome Scale and a return to driving questionnaire. The latter gathered information concerning demographic and clinical variables, including disorders of consciousness, posttraumatic amnesia and the consumption of psychotropic drugs. The groups were compared by analyzing the risk of a road traffic accident before versus after injury as well as in relation to the overall distance driven.

There was no significant difference between groups in the number of subjects involved in road accidents or the number of accidents before and after injury. However, when looking at the number of accidents per miles driven, the participants had a 3.38 times greater risk of being involved in a road accident after a TBI than before. The percentage of accidents in which the subject was responsible was 47% before and 67% after the brain injury ( $p < 0.02$ ).

**Conclusion:** This study of patients with a severe traumatic brain injury found that, among those who resume driving, there is a significant increase in the risk of being involved in a motor vehicle accident per mile driven, and an increased risk of being at fault for the accident.

Bivona, U., et al. Return to Driving After Severe Traumatic Brain Injury: An Increased Risk of Traffic Accidents and Personal Responsibility. **J Head Trauma Rehabil.** 2012, May/June; 27: 210-215.

### WEIGHT GAIN AFTER CHILDHOOD TRAUMATIC BRAIN INJURY

Several studies have documented anthropometric measures after childhood brain injury. One author found a higher prevalence of overweight and obesity among children who were chronically brain injured. This study was designed to better assess the effects on weight gain of brain injury in children.

This observational investigation targeted patients ages zero to 15

years with a traumatic brain injury (TBI) requiring intensive care hospitalization. This study included all children admitted over a one-year period with diagnoses of TBI. The patients were followed for health and anthropometric data for 12 months after the TBI. Height and weight were measured by trained nurses during the patient's hospitalization and then during follow-up visits. Using these data, body mass index (BMI) was calculated.

During the study period, 39 consecutive children were recruited to the study. The median age was eight years, seven months, with the TBI rated as severe in 25 of the cases. The median length of hospital stay was 21 days, and that in rehabilitation 310 days, including both inpatient and outpatient care. The mean intelligence quotient one year after injury was 81. The sample's mean BMI increased by 0.9 kg/m<sup>2</sup>. The rate of increase was higher in males than in females. Further, the rate of increase was greater among those unable to walk ( $p = 0.014$ ) and those of older age ( $p = 0.011$ ).

**Conclusion:** This longitudinal study of children hospitalized for traumatic brain injury found that, in the first year after injury, patients gain an average of 0.9 kg/m<sup>2</sup> in body mass index.

Jourdan, C., et al. Weight Gain after Childhood Traumatic Brain Injury: A Matter of Concern. **Develop Med Child Neurol.** 2012, July; 54(7):624-628.

### BOTOX FOR SPASTICITY IN SEVERE BRAIN INJURY

A common symptom of severe traumatic brain injury (TBI) is spasticity. While systemic medications may be effective, these drugs are often limited in use by their side effect profile. Botulinum toxin-A (BT-A), combined with rehabilitation, has been found to be helpful in the treatment of TBI related tone disorders, although many studies have short follow-up periods. This study evaluated the efficacy and safety of BT-A injections in patients with severe TBI related spasticity.

This study involved 21 patients diagnosed with severe acquired brain injury, all admitted for rehabilitation services. All had brain injury related focal spasticity, with pain impairing either active or passive stretching.

Each subject was also noted to have a lack of adequate improvement after oral anti-spasmodic medications. All patients were assessed at admission with the Barthel index and a modified Ashworth score. Pain was measured with a visual analogue scale during active and passive stretching.

At one month after hospital admission, the evaluations were repeated, with those showing no significant improvement treated with BT-A at a maximum dosage of 600 units in the muscles of the upper and/or lower limbs. Following injections, rehabilitation continued, including passive or active stretching and occupational therapy. All patients were prospectively evaluated at 12-month follow-up following the first injection. During this time the participants were repeatedly treated with BT-A at not less than three months between injections. According to the clinical response, all patients were injected at least twice through the one-year follow-up.

The mean period between injections was 4.7 months. The Ashworth scores were lower at both the second and last injections than at baseline ( $p < 0.0001$ ). Barthel index scores were also significantly improved between baseline and the final evaluation ( $p < 0.0001$ ). Visual analogue scale scores improved, with the reduction of scores after each injection ( $p < 0.0001$ ). Findings revealed no cases of side effects attributed to the injections.

**Conclusion:** This study of patients with spasticity after acquired, severe brain injury demonstrated that BT-A is effective for long-term management, with better outcomes among those treated earlier after spasticity onset.

Clemenzi, A., et al. Care Management of Spasticity with Botulinum Toxin A in Patients with Severe Acquired Brain Injury: A One-Year Follow-Up Prospective Study. **Brain Injury.** 2012, July; 26(7-8): 979-983.

#### **ASPIRIN FOR RECURRENT THROMBOEMBOLISM**

Previous studies have demonstrated that, among patients with unprovoked venous thromboembolism, 20% experience a recurrence within two years after prophylaxis is discontinued. As aspirin has been shown to be of

benefit in reducing this risk, this study assessed the clinical benefit of aspirin therapy after completion of treatment with vitamin K antagonists.

This multi-center, double-blind, randomized trial included patients 18 years of age and older who had been treated for a first-ever, symptomatic, unprovoked proximal deep vein thrombosis, pulmonary embolism or both. Subjects were randomized to receive either aspirin at 100 mg daily or placebo for two years after completion of therapy with a vitamin K antagonist. The primary efficacy outcome was a symptomatic, objectively confirmed, recurrent venous thromboembolism. Secondary efficacy outcomes included nonfatal myocardial infarction, unstable angina, stroke, transient ischemic attack, acute ischemia of the lower limbs and death from any cause. The principal safety outcome was major bleeding.

A total of 403 patients were randomly assigned, with 205 receiving aspirin and 197 receiving placebo. A recurrent venous thromboembolism occurred in 71 patients, with deep vein thrombosis in 44 and pulmonary embolism in 27. The primary outcome occurred in 28 of those who received aspirin and in 43 of those who received placebo ( $p = 0.02$ ). Independent risk factors for recurrent venous thromboembolism included age of more than 65 years and male gender ( $p = 0.02$  and  $p = 0.01$ , respectively). Two episodes of nonfatal major bleeding were documented, one in each group. No significant differences were found in secondary outcome measures between the two groups.

**Conclusion:** This study of patients with a history of unprovoked venous thromboembolism found that aspirin, dosed at 100 mg per day, can reduce the rate of recurrence by 40%, with no increased risk of major bleeding.

Becatinni, C., et al. Aspirin for Preventing the Recurrence of Venous Thromboembolism. **N Engl J Med.** 2012, May 24; 366(21): 1959-1967.

#### **EXCESSIVE DAYTIME SLEEPINESS AND VASCULAR EVENTS**

Excessive daytime sleepiness is among the most frequent sleep complaints, affecting up to 30% of adults over 65 years of age. This

study investigated the association between the frequency of excessive daytime sleepiness and vascular morbidity in community dwelling, older individuals.

The study included 9,294 community dwellers, 65 years of age or older, selected from the electoral rolls of three French cities. Interviewers conducted face-to-face interviews using a standardized questionnaire, with information gathered including demographic characteristics, education, occupation, daily lifestyle habits and functional status. Patients were assessed for instrumental activities of daily living, cognitive function, symptoms of depression and past medical history, including cardiovascular history. At baseline, the subjects self-rated the occurrence of sleep disorders, including excessive sleepiness, rating their sleep quality as good, average or poor. All medications were recorded, including sleep medications. At each two-year follow-up visit, the subjects were asked to report any new, severe medical event or hospitalization.

At a median follow-up of 5.1 years, 372 subjects experienced a first vascular event, including either a stroke or congestive heart disease (CHD). Compared to subjects without excessive daytime sleepiness, at baseline, subjects with frequent excessive daytime sleepiness had a twofold increase in the risk of CHD and stroke combined. This included a 2.24 fold increase in the risk of stroke and a 1.7 fold increase in the risk of CHD.

**Conclusion:** This study of community dwelling elderly found that individuals with self-reported excessive daytime sleepiness had a significant increase in the risk of congestive heart disease and stroke.

Blanchier, M., et al. Excessive Daytime Sleepiness and Vascular Events: The Three-City Study. **Ann Neurol.** 2012 May; 71(5): 661-667.

#### **BRAIN INJURY RELATED DYSAUTONOMIA TREATED WITH INTRATHECAL BACLOFEN**

Dysautonomia is a clinical syndrome with symptoms including profuse sweating, tachycardia, high blood pressure, muscle hypertonicity, hyperthermia, tachypnea, bronchial hyperstimulation and hypersialosis. While most often self-limiting,

dysautonomia can interfere with a patient's comfort and rehabilitation efforts. While intrathecal baclofen has been found effective for supra-spinal spasticity, little evidence-based treatment has been offered to address dysautonomia. This study investigated the long-term effects of intrathecal baclofen on the symptoms of dysautonomia and hypertonia.

Subjects included 45 patients with severe traumatic brain injury (TBI), all of whom had received intrathecal baclofen pumps for severe hypertonia associated with symptoms of dysautonomia. Each had failed conservative treatment, with surgical implantation of the pump indicated after a test dose of intrathecal baclofen. All subjects were assessed with the Coma Recovery Scale-Revised (CRS-R), the Barthel index, the Glasgow Outcome Scale, the Ashworth scale, a hypertonic episode score, a sweating episode score and a voluntary motor response score.

Forty-three patients were available for long-term evaluation. Group 1 had a maximum CRS-R score of at least 23, while Group 2 had a maximum CRS-R score of below 23. At ten-year follow-up, 21% had died, 30.2% were severely disabled or demonstrated unresponsive wakefulness syndrome and 49% had a good recovery of consciousness. The symptoms of dysautonomia, hypertonia and voluntary motor responses improved significantly, with greater improvement in group 1 than group 2. Treatment related complications requiring hospitalization occurred in 63% of the patients.

**Conclusion:** This study of patients with severe traumatic brain injury demonstrates that, after intrathecal baclofen pump placement, symptoms of dysautonomia improve significantly.

Hourau, X., et al. A Ten-Year Follow-Up Study of Patients with Severe Traumatic Brain Injury and Dysautonomia Treated with Intrathecal Baclofen Therapy. *Brain Injury*. 2012, July; 26(7-8): 927-940.

### CAUSES OF DEATH IN PATIENTS WITH MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is associated with a higher mortality rate than that of the general population. Despite the numerous studies that have reviewed the causes of death in

patients with MS, the influence of lifestyle parameters has not been well studied. This study was designed to estimate mortality rates of patients with MS, in an effort to determine the influence of lifestyle parameters on specific causes of death.

This retrospective cohort study was conducted using the British General Practice Research Database (GPRD), linked to the National Hospital Episode Statistics and national death certificates. The GPRD provides detailed information concerning demographics, drug prescriptions, clinical events, specialist referrals and hospital admissions. The cohort included all patients at least 18 years of age, diagnosed with MS between 2001 and 2008. Patients were followed from the index date of MS diagnosis to the end of data collection, when those patients were transferred out of the practice or upon patient's death, whichever occurred first.

Compared to age, gender, and practice matched controls, a significantly increased risk for all cause mortality was found in patients with MS (hazard ratio of 3.51). In patients with MS, infectious and respiratory diseases were found to be the most common diseases related to death (58%). Among those who died from acute respiratory infections, a significantly higher proportion were current smokers, but not ex-smokers. A body mass index of less than 20 kg /m<sup>2</sup> was associated with an increased risk.

**Conclusion:** This British study found that patients with multiple sclerosis have a 3.5 fold increase in risk of death compared with the general population. The greatest risk involves respiratory disease, magnified by tobacco abuse.

Lalmohamed, A., et al. Causes of Death in Patients with Multiple Sclerosis and Matched Referent Subjects: A Population-Based, Cohort Study. *European J Neurol*. 2012; 19: 1007-1014.

### CIRCUIT TRAINING AFTER STROKE

After a stroke, an estimated 25 to 74% of survivors require some assistance with daily activities. Walking is affected in as many as 80% of patients. As recent meta-analyses have shown that patients trained with circuit training can gain benefits in mobility, this study

investigated the use of this intervention as an alternative to usual physiotherapy after stroke.

This stratified, multicenter, single-blind, randomized, controlled trial included all patients with stroke presenting at nine participating study centers. Eligible patients were able to walk a minimum of 10 m without physical assistance, were discharged home from a rehabilitation center, and needed to continue outpatient care to improve walking. Subjects in the intervention group participated in a 90-minute, graded, task oriented circuit training program twice a week for 12 weeks. Training utilized eight work stations, intended to improve performance of meaningful tasks related to walking competency. At each station participants worked in pairs, with one performing the task for three minutes and the other observing. The roles were then switched. Those in a control group received usual outpatient physiotherapy, designed to improve control of standing balance, physical condition and walking competency, provided according to Dutch physiotherapy guidelines. The primary outcome measure was the Mobility domain of the Stroke Impact Scale. Secondary outcomes included other domains of the Stroke Impact Scale, the Rivermeade Mobility Index, the Falls Efficacy Scale, the Nottingham Extended Activities of Daily Living Scale, the Hospital Anxiety and Depression Scale and the Fatigue Severity Scale. Also included were several performance tests.

Of the 250 patients randomized, 126 were assigned to circuit training and 124 to usual care. For the primary outcome measure, no significant difference was found between the two groups (p=0.94). The circuit training group performed better on the five meter comfortable walking speed test (p<0.001), the six minute walk test (p=0.007), and the modified stairs test (p=0.015) during the intervention phase. More patients in the circuit training group showed a clinically meaningful change beyond 50 meters on the six minute walk test (p=0.06).

**Conclusion:** This study of patients with acute stroke found that task oriented circuit training within the first six months is as effective as individually tailored physical therapy in improving mobility among patients with mild to moderate stroke.

Van de Port, I., et al. Effects of Circuit Training as Alternative to Usual Physiotherapy after Stroke: Randomized, Controlled Trial. **BMJ**. 2012; 344:e2672

### SUNLIGHT AND DECREASED RISK OF MULTIPLE SCLEROSIS

Ultraviolet radiation exposure, vitamin D status, tobacco abuse and Epstein-Barr virus infection are considered to be major influences on the risk of developing multiple sclerosis (MS). There is evidence that frequent exposure to ultraviolet radiation confers a protective effect against developing MS. Vitamin D is thought to be a mediator of this effect. An interaction between the human leukocyte antigen HLA-DRB1\*15 and vitamin D has recently been proposed. This study examined the interaction between HLA-DRB1\*15 and previous exposure to ultraviolet radiation and vitamin D levels in the onset of MS.

This study relied upon data collected from the Epidemiological Investigation of Multiple Sclerosis (EIMS), an ongoing case control study in geographically defined parts of Sweden. In this study, a case was defined as a person receiving a first-time diagnosis of MS. For each case, two matched controls were randomly selected from the national population register. Information regarding environmental exposures among cases and controls was collected by questionnaire. Vitamin D level was established by blood sample, with genotyping completed in a subset of the cases and controls. The potential interaction between ultraviolet radiation exposure and vitamin D with HLA-DRB1\*15 was assessed.

The analysis included 1,013 cases and 1,194 controls. A significant, inverse relationship was found between exposure to ultraviolet radiation and the risk of developing MS. Adjustment for vitamin D only marginally changed the estimated association. A significant relationship was found between exposure to ultraviolet radiation and vitamin D levels for both women and men. Subjects with vitamin D levels of less than 50nM/l were at an increased risk for MS, with an odds ratio of 1.4. No interaction was found between either ultraviolet radiation exposure or levels of vitamin D and the HLA-DRB1\*15 allele.

**Conclusion:** This large, population-based study provides

further evidence that ultraviolet radiation exposure and vitamin D affect the risk of multiple sclerosis. No significant association was found between these factors and the status of the HLA-DRB1\*15 antigen.

Baarnhielm, M., et al. Sunlight is Associated with Decreased Multiple Sclerosis Risk: No Interaction with Human Leukocyte Antigen-DRB1\*15. **Euro J Neur**. 2012, July; 19(7): 955-962.

### TAI CHI AS A COMMUNITY-BASED FALL PREVENTION

Previous studies of fall prevention strategies have suggested that tai chi may be useful in reducing fall rates among the elderly. This study sought to determine whether a government subsidized New Zealand program of tai chi exercise is effective in reducing falls in community dwelling, older adults.

This New Zealand, multi-center, randomized, controlled trial included participants recruited from the community through local media. Subjects were 65 years of age or older and had experienced at least one fall in the previous year, or were considered to be at risk for falling. After baseline assessment, participants were randomly assigned to one of three study groups: those participating in tai chi once per week, those participating in tai chi twice per week, or a control group using lower limb exercise once per week. The tai chi classes lasted for one hour, for 20 weeks. The lower extremity program involved seated exercises, including stretching, low-level strength and low-level cardiovascular exercise. The primary outcome measure was the number of falls sustained during the 20-week intervention and over a 12-month follow-up period. Secondary outcomes included mobility, balance and leg strength.

Among the 684 participants, 1,060 falls were reported. Falls occurred in 59.5% of the once per week tai chi group, in 53.1% of the twice per week tai chi group and in 65.1% of the low-level exercise group. Frequent fallers, defined as those falling more than twice, were found in 25.2% of the tai chi once per week, 15.3% of the tai chi twice per week and 22.3% of the low-level exercise groups. While there was a 58% reduction in the mean fall rate for all groups across the entire study period, the

differences between groups did not reach statistical significance.

**Conclusion:** This prospective study of elderly, community dwelling adults found a greater reduction in falls among patients who participated in twice per week tai chi exercise. This difference did not however reach statistical significance.

Taylor, D., et al. Effectiveness of Tai Chi as a Community-Based Fall Prevention Intervention: A Randomized, Controlled Trial. **JAGS**. 2012, May; 60(5): 841-848.

### ECCENTRIC TRAINING FOR SUBACROMIAL IMPINGEMENT

Disorders of the rotator cuff are among the most common causes of shoulder pain. The supraspinatus tendon is the most frequently affected structure among patients with subacromial impingement, due to its position in the subacromial space. As treatment strategies in patella and Achilles tendinopathy have revealed that eccentric training can not only improve function, but also repaired tendon tissue, this study explored the use of this strategy for treatment of supraspinatus tendinopathy.

Subjects were enrolled from an orthopedic surgery practice and included 61 patients diagnosed with subacromial impingement. The subjects were randomized to either a traditional rotator cuff strengthening training (TT) group or a TT group combined with heavy load eccentric training (TT & ET). The TT group performed traditional rotator cuff strengthening exercises at home, including internal and external rotation resistance with an elastic band. Each exercise was performed once a day for three sets of 10 repetitions. In the combined group, the same exercises were performed, with the addition of eccentric training involving a dumbbell weight, with three sets of 15 repetitions performed twice a day. When pain was no longer present during the last set of repetitions, the weight was increased by 1/2 kg. All patients completed a daily log book to record pain. Outcome was assessed at baseline and at six and 12 weeks, with the primary outcome measure, the SPADI questionnaire, used to evaluate pain and function.

Both groups demonstrated a significant increase in isometric strength over time. *Post hoc* analysis revealed a significant increase in

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strength from zero to six weeks, but not from six to 12 weeks. Both groups realized improvements in pain and function, as measured by the SPADI, with no significant difference seen between the two groups. Isometric shoulder abduction strength at 90° was the only significant difference between the two groups, favoring the combined treatment group.

**Conclusion:** This study demonstrated that adding heavy load eccentric training to the rehabilitation of patients with subacromial impingement can increase isometric strength at 90° of scapular abduction, but does not decrease pain or improve function more than traditional therapy.

Maenhout, A., et al. Does Adding Heavy Load Eccentric Training to Rehabilitation of Patients with Unilateral Subacromial Impingement Result in Better Outcome? A Randomized, Clinical Trial. *Knee Surg Sports Traumatol Arthrosc.* 2012, DOI: 10.1007/s00167-012-2012-8.

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