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## PR 0051 THERAPY FOR MUSCULAR DYSTROPHY

Duchenne's muscular dystrophy (DMD) is caused by mutations in the dystrophin gene leading to dystrophin deficiency at the myofiber membrane and continued fiber degeneration. A promising repair strategy for this disorder involves antisense oligonucleotides that induce specific exon skipping during pre-messenger RNA splicing. Local intramuscular administration of the antisense oligonucleotide PR 0051 was previously found to induce the skipping of exon-51 during pre-messenger RNA splicing of the dystrophin gene, and to facilitate new dystrophin expression in muscle fiber membranes. This study assessed the safety, pharmacokinetics and effects of systemically administered PR 0051.

Patients diagnosed with DMD, all five to 16 years of age, were recruited for this open label, dose escalation study. Twelve subjects were randomized to receive weekly abdominal subcutaneous injections of PR 0051, from 0.5 to 10 mg per kg of body weight for five weeks. The primary outcome variables were assessments of safety. Secondary outcomes included pharmacokinetics and molecular/clinical effects, measured at regular intervals. Muscle biopsy at the tibialis anterior was performed at baseline and at two weeks after the last dose.

No serious events were reported during this trial, with the most common found to be mild reactions at the injection site, as well as mild proteinuria and increased urinary  $\alpha$ 1 microglobulin levels. PR 0051 induced detectable, specific exon-51 skipping at doses of 2.0 mg or more per kg. New dystrophin expression was observed in between 60% and 100% of muscle fibers in 10 of the 12 patients. After 12 weeks improvement was clinically seen in the distance walked in six minutes, with a mean

improvement of 35.2 meters. Three patients demonstrated an improvement of 65 meters or more.

**Conclusion:** This gene therapy study of patients with Duchenne's muscular dystrophy found that the administration of the antisense oligonucleotide, PR 0051, resulted in a dose dependent, abundant expression of dystrophin in muscles distant from the injection site. This phenomenon was accompanied by a modest improvement in six-minute walking distance.

Goemans, N., et al. Systemic Administration of PR0051 in Duchenne's Muscular Dystrophy. **N Eng J Med.** 2011, April 21; 364(16): 1513-1522.

## LOW LASER FOR SUBACROMIAL SYNDROME

Pain is the primary symptom in most patients with shoulder disorders affecting soft tissue. A common cause of pain is the subacromial syndrome, which includes rotator cuff and biceps tendinitis, calcifying tendinitis, subacromial bursitis and rotator cuff rupture. This study was designed to evaluate the effect of Low Level Laser Therapy (LLLT), combined with exercise, for the treatment of this syndrome.

This randomized, controlled trial included 80 patients who presented with clinical evidence of the subacromial syndrome. All were assessed using the Neer sign, the Hawkins Kennedy Test, the Jobe Test and the Speed Test. The subjects were randomly assigned to receive LLLT and exercise or to receive a placebo laser with the same exercise. All participants were treated for 10 sessions. The LLLT group underwent treatment with a wavelength of 890 nm in pulsed mode, delivered at the coracoids, the glenohumeral joint and the rotator cuff tendon for a total of six minutes.

The biceps tendon was treated in those with symptoms of biceps tendinitis. Outcome measures were pain and shoulder range of motion.

After treatment, both groups showed improvements in shoulder range of motion and pain severity. The laser treatment group enjoyed significantly greater improvements in active and passive range of motion, as well as in pain severity ( $p=0.00$ ,  $p=0.00$ , and  $p=0.00$  respectively).

**Conclusion:** This study of patients with subacromial syndrome demonstrates that the addition of low level laser therapy to traditional physical/occupational therapies can accelerate the therapeutic outcome of the intervention.

Abrisham, S., et al. Additive Effects of Low-Level Laser Therapy with Exercise on Subacromial Syndrome: A Randomized, Controlled Trial. **Clin Rheum.** 2011, May 4: DOI 10.1007/S10067-1011-1757-7.

## GROWTH HORMONE AND THE PROLIFERATIVE RESPONSE OF THE HIPPOCAMPUS AFTER BRAIN INJURY

Acute injury to the central nervous system may be followed by enhanced neural progenitor cell proliferation and neurogenesis. As adult neurogenesis is regulated by the growth hormone, insulin like growth factor-I (IGF-1), this study investigated the effect of growth hormone treatment on the proliferation of exogenous neural progenitor cells after induced brain injury.

This animal study included adult rats, 9- 10 weeks of age, randomized to receive an intraperitoneal injection of either Kainic acid (KA) or saline. The subjects were administered growth hormone treatment lasting four days, beginning immediately or 10 days after the administration of KA. Proliferating cells were immunodetected after labelling by

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administration of 5-bromodeoxyuridine (BrdU), given for four days before sacrifice. GH expression was detected by *in situ* hybridization and immunofluorescence.

The administration of KA induced seizure activity, followed by a significant increase in the number of hippocampal cell precursors. This effect was significantly enhanced by treatment with growth hormone. In addition, hippocampal growth hormone expression was up-regulated after the administration of KA. Among those animals receiving the growth hormone at ten days, no significant differences in the number of BrdU-positive cells were observed in the hippocampi of KA-treated rats as compared with saline-treated rats.

**Conclusion:** This animal study of induced neuronal death revealed that treatment with growth hormone results in a proliferation of precursor cells in the hippocampus.

Devesa, P., et al. Growth Hormone (GH) Treatment May Cooperate with Locally-Produced GH in Increasing the Proliferative Response of Hippocampal Progenitors to Kainate-Induced Injury. *Brain Inj.* 2011, May; 25(5): 503-510.

### **MEDICAL ERRORS AND TIME OF ADMISSION TO STROKE REHABILITATION**

Very few studies have investigated the rate of medication errors as a function of patient arrival time at an inpatient rehabilitation facility. This study assessed the medication ordering error frequency and the length of hospital stay among patients admitted with a stroke to an inpatient rehabilitation service at different times of day.

Sixty patients, admitted with a diagnosis of stroke for inpatient acute rehabilitation, were identified for this study. Thirty who arrived before 4 p.m. were identified as group I, and 30 who arrived after 4 p.m. were identified as group II. The two groups were compared across outcome variables, including frequency of admission medication errors and length of hospital stay. For hospital length of stay, the groups were compared against the mean length of stay for all patients at the facility.

The mean frequency of admission medication ordering errors was 0.17 errors per patient among those arriving before 4 p.m. and 0.67 errors per patient among those arriving after 4 p.m. ( $p=0.028$ ). The mean hospital length of stay for those who arrived before 4 p.m. was 13.4 days, while that for those who arrived later was 19.9 days ( $p=0.0035$ ).

**Conclusion:** This study found a significant difference in medication errors and hospital length of stays, favoring patients who were admitted before 4 p.m. over those admitted later.

Pitts, E., et al. Medication Errors versus Time of Admission in a Subpopulation of Stroke Patients Undergoing Inpatient Rehabilitation: Complications and Considerations. *Topics in Stroke Rehab.* 2011, March-April: 151-153.

### **TRANSCRANIAL MAGNETIC STIMULATION FOR POST-STROKE SPASTICITY**

Spasticity in stroke patients is treated with oral medications, peripheral nerve or intramuscular injections and/or intrathecal baclofen. Recently, some groups have reported beneficial effects of low-frequency repetitive transcranial magnetic stimulation (rTMS), applied to the non-lesioned hemisphere. This study was designed to determine the efficacy of inpatient intervention with low-frequency rTMS for upper limb spasticity due to stroke.

Subjects were 39 post-stroke patients with spastic upper limb hemiparesis. The mean age at admission was 56.5 years, and the average time since stroke was 50.3 months. All participants were hospitalized for 15 days to receive a combination of rTMS and occupational therapy (OT). During admission, each patient received 22 treatment sessions of low-frequency rTMS and OT. One or two sessions of treatment were provided daily, excluding Sundays. One session consisted of 1,200 pulses lasting 20 minutes. The intensity of stimulation was set at 90% of the motor threshold of the muscle. The OT sessions included shaping techniques and repetitive task practice techniques. Spasticity and motor function of the affected a limb were evaluated on the day of admission, at discharge and at

four weeks post-discharge. Spasticity was measured with the modified Ashworth scale, with each subject also tested with the Fugl-Meyer Assessment and the Wolf Motor Function Test.

The 15-day course of treatment resulted in significant decreases in modified Ashworth scale scores for finger flexors, both at discharge and at four weeks post-discharge ( $p < 0.01$  and  $p < 0.05$ , respectively). Similar results were found for wrist flexors, both at discharge and at four weeks post-discharge ( $p < 0.005$  and  $p < 0.05$ , respectively). Significant increases were also noted in both Fugl-Meyer Assessment and Wolf Motor Function Test scores.

**Conclusion:** This study of patients with chronic stroke found that a 15-day treatment with low-frequency repetitive transcranial magnetic stimulation reduced spasticity and improved motor function of the affected upper extremity.

Kakuda, W., et al. Anti-Spastic Effect of Low-Frequency rTMS, Applied with Occupational Therapy in Post-Stroke Patients with Upper Limb Hemiparesis. **Brain Inj.** 2011, May; 25(5): 496-502.

### **SUBPAR UTILIZATION OF DENTAL CARE AMONG AMERICANS WITH A HISTORY OF STROKE**

Chronic, low-level infection has been found to accelerate atherosclerosis. Periodontitis, the chronic inflammation of tissue surrounding and supporting the teeth, is significantly more common in patients with atherosclerosis. It is generally believed that poor oral hygiene leads to periodontitis and promotes atherosclerosis. This study assessed the use of dental care among adult patients with stroke in the United States.

Data for this study were obtained from the National Health Interview Survey (NIHS), sponsored by the Centers for Disease Control and Prevention (CDC). The present analysis used data from the Family Core, Person file and from the Sample Adult Core, Adult file from the 2006 NIHS survey.

A total of 24,275 persons, 18 years of age or older were interviewed. Stroke survivors were identified, with demographic

characteristics reviewed. Data were reviewed to determine whether the survivor had visited a dentist at least once during the previous 12 months. Data were compared between those who had seen a dentist within the previous 12 months and those who had not.

Of the 24,275 adults included in the 2006 survey, 59.8% reported having seen a dentist within the prior 12 months. Among those identified with a stroke, 46% reported having seen a dentist within the past 12 months. Factors independently associated with a dentist visit were female gender, being married, high school or greater education, and having had contact with a primary care doctor in the previous year. Factors independently associated with not visiting a dentist were black race and the presence of a significant medical comorbidity.

**Conclusion:** This study demonstrates that individuals who have a history of stroke visit the dentist less frequently than do those in the general population.

Sanossian, N., et al. Subpar Utilization of Dental Care among Americans with a History of Stroke. **J Stroke Cerebrovasc Dis.** 2011, May-June;20(3):255-259.

### **ENHANCING RECOVERY FROM ACUTE ISCHEMIC STROKE WITH DONEPEZIL**

While 10% of patients with a first stroke have dementia at the time of the stroke, 10% develop new dementia soon after the stroke. More than one third have dementia after a recurrent stroke. Pilot trials have suggested that enhancement of the cholinergic system with donepezil may improve post-stroke aphasia and upper limb dysfunction. This study assessed the safety and tolerability of early donepezil treatment after acute ischemic stroke.

This prospective trial included adults treated with donepezil within 24 hours of a definite or probable acute ischemic cerebrovascular accident. Study participants received donepezil, 5 mg per day for 30 days, and, if tolerated, were increased to 10 mg per day for 60 additional days. Outcome measures included treatment related adverse events and side effects. The primary, favorable outcome variable was a 90-day

National Institutes of Health Stroke Scale score of less than one.

Enrollment extended from November of 2008 through April of 2010. Of the 33 participants, 25 completed the 90-day course of therapy. Reasons for discontinuation included side effects ( $n=3$ ), death ( $n=2$ ), referral to palliative care ( $n=1$ ), medication not provided at discharge from rehabilitation ( $n=1$ ) and loss to follow-up ( $n=1$ ). The most frequent side effects were fatigue, nausea, depression and insomnia. Favorable outcomes were more frequent among those treated with donepezil than among severity matched controls.

**Conclusion:** This pilot study of patients with acute ischemic stroke treated with donepezil within 24 hours of stroke onset found that the treatment was safe and tolerated, with the results also suggesting improved functional outcome.

Barrett, K., et al. Enhancing Recovery after Acute Ischemic Stroke with Donepezil as an Adjuvant Therapy to Standard Medical Care: Results of a Phase II-A Clinical Trial. **J Stroke Cerebrovasc Dis.** 2011, May/June;20(3): 177-182.

### **PERMANENT POST-CONCUSSIVE SYMPTOMS**

Some have estimated that approximately half of those patients with mild head injury will be affected by a cluster of cognitive, somatic and emotional symptoms of some duration. However, few studies have explored post-concussive symptoms beyond one year. This study investigated the population of patients with chronic or permanent post-concussive symptoms.

All patients referred to a community head injury service for treatment of persistent post-concussive syndrome following a mild head injury (MHI) were identified through clinical records. Participants were required to have sustained a mild head injury at least 18 months prior to the study, and to have at least three, current post-concussive symptoms. Consenting participants were sent five questionnaires concerning quality of life, affect, stress and pain levels. In addition, face-to-face examinations were arranged to administer 11 cognitive tests.

Twenty-four participants were included in this study, with a mean time since the injury of 6.9 years. No significant relationship was found between age and severity of post-concussive symptoms, or between time since the injury and severity of symptoms. Those with persistent symptoms were characterized by older age, higher levels of post-concussive symptoms, and a high prevalence of anxiety and depression and measurable cognitive deficits. Approximately 92% of the sample were employed at the time of injury, while only 50% were employed at follow-up.

**Conclusion:** This study of patients with mild head injury and persistent cognitive symptoms found that these symptoms are associated with measurable cognitive deficits, older age, high levels of anxiety, and high post-injury unemployment.

King, N., et al. Permanent Post-Concussion Symptoms after Mild Head Injury. *Brain Inj.* 2011, May; 25 (5): 462-470.

#### **LONG-TERM MUSCULOSKELETAL COMPLAINTS AFTER TRAUMATIC BRAIN INJURY**

Traumatic brain injury (TBI) is a leading cause of death and disability in persons under the age of 45 years in the United States. Most of the recovery from TBI is thought to take place within the first two years after injury. This study sought to quantify the extent and impact of musculoskeletal complaints in patients who survive a TBI.

Patients were identified by reviewing consecutive medical records of persons who had been hospitalized for a moderate to severe TBI, 15 years or more prior. A response rate of 49% was achieved among those individuals who were successfully traced and met the study eligibility requirements. Study participants' musculoskeletal complaints were screened through the administration of two validated instruments during a telephone interview. The mean age at follow-up was 48 years, while the mean time post-injury was 26 years.

Of the patients contacted, 34 agreed to an interview. Of those, 79% reported having experienced some musculoskeletal complaints during the previous 30 days. That

finding was found to be greater than the rate of 17% reported by the same age group (45 to 54 years) in the general population in Canada. Of the group reporting musculoskeletal complaints, 67% reported having been told by a physician that they had some form of arthritis, gout, lupus or fibromyalgia. Widespread pain (defined as axial pain plus at least two other regions of pain) was the most common pain pattern reported.

**Conclusion:** This study of patients who had received inpatient rehabilitation for a moderate to severe traumatic brain injury found that, years later, the majority had musculoskeletal complaints.

Brown, S., et al. Long-Term Musculoskeletal Complaints after Traumatic Brain Injury. *Brain Inj.*, 2011, May; 25(5): 453-461.

#### **EDARAVONE FOR ACUTE STROKE**

Stroke is the leading cause of adult disability in the United States and Europe, as well as the second most common cause of death worldwide. To date, the only approved treatment for ischemic stroke is intravenous recombinant tissue plasminogen activator. This drug has a very narrow treatment window. Edaravone is a potent, novel, free radical scavenger that inhibits hydroxyl radicals and free radical-mediated lipid peroxidative damage. This study was designed to gain further insight into the protective effects of edaravone on delayed neural death in the hippocampus.

This animal study involved adult rats, divided to receive surgery with placebo/vehicle, surgery plus edaravone or a sham surgery without artery occlusion. Surgical cerebral ischemia was induced by right middle cerebral artery occlusion. All subjects underwent reperfusion after 60 minutes. All rats were assessed at three, seven and 30 days after occlusion.

In the edaravone treated group, the loss of neurons in the pyramidal layer of the hippocampus was significantly reduced at all time points tested. On tests of cognitive function, the treatment group behaved better than did the sham group. Also noted in the treated group were markedly decreased malondialdehyde levels,

increased superoxide dismutase levels and reduced levels of inflammatory cytokines.

**Conclusion:** This animal study of acute ischemic stroke found that edaravone exhibits a neuro-protective effect on the hippocampus as a result of its ability to inhibit inflammation, suppress astrocyte activation and to scavenge free radicals.

Jiao, L., et al. Edaravone Alleviates Delayed Neuronal Death and Long-Dated Cognitive Dysfunction of Hippocampus after Transient Focal Ischemia in Wistar Rat Brains. *Neurosci.* 2011, May; 182: 177-183.

#### **RECOVERY FROM ACHILLES TENDINOPATHY**

Achilles tendinopathy is associated with activities such as running and jumping, and is highest among middle-aged individuals. Eccentric exercise is thought to be the most effective for treating the mid-portion of the Achilles. This study assessed the five-year outcomes of patients treated for this disorder with exercise.

This prospective trial included men and women ages 20 to 60 years with Achilles tendinopathy pain of more than two months' duration. Of the 38 patients included in the original study, 34 were available for five-year follow-up. All subjects were treated with a program of progressive Achilles tendon loading and strengthening program for 12 weeks to six months, monitored by a physical therapist. The exercises included one legged and two legged eccentric exercise, as well as fast rebounding heel rises.

The participants were divided into three groups based upon their levels of symptoms at the time of five-year follow-up. These included fully recovered with no symptoms (ASYMP), fully recovered with new symptoms (NEWSYMP) and not fully recovered with continuous symptoms (CONSYMP). Five-year evaluations included questionnaires and a test battery.

No significant differences were seen in the numbers of patients with no symptoms, new symptoms or continued symptoms. All subjects reported satisfaction with the original treatment, with 80% reporting full recovery, 65% reporting no symptoms and 15% reporting new

symptoms. Of the seven patients reporting continued symptoms, three had minimal symptoms. There was no significant difference in any of the groups between the reported physical activity levels before injury and the levels at the 5-year follow-up.

**Conclusion:** This long-term study of patients with Achilles tendinopathy found that the majority recover from both functional loss and symptoms with exercise alone.

Silbernagel, K., et al. The Majority of Patients with Achilles Tendinopathy Recover Fully when Treated with Exercise Alone. *Am J Sports Med.* 2011, March; 39(3): 607-613.

### **ADHESIVE CAPSULITIS TREATMENT: PREDICTORS OF OUTCOME**

Adhesive capsulitis is most often treated with a multimodal program emphasizing home exercise, with or without supervised therapy, and often with intra-articular or oral corticosteroids. Operative treatment is usually reserved for patients with persistent pain and clinically relevant motion deficits, despite a lengthy non-operative program. This study evaluated the efficacy of non-operative and operative treatment in a large group of patients.

This retrospective study identified 99 patients with adhesive capsulitis, seen over a three-year period. Of those, 85 completed a self-assessment survey at a minimum of 24 months' follow-up. The mean duration of symptoms before initial presentation was eight months. All but three patients participated in supervised physiotherapy and home exercise for an average of nine weeks. The subjects were also instructed to perform their exercises at home three times daily. Each participant was offered a corticosteroid injection at initial presentation if pain prevented participation in the stretching program, or at four to six weeks if the initial treatment was unsuccessful.

Twenty-four patients (25 shoulders) underwent operative intervention, at a minimum of 12 weeks after initial presentation. After surgery all subjects used a continuous passive motion chair for one to three weeks. Shoulder function was self-assessed with the Simple Shoulder Test (SST) at baseline and

final follow-up, and with the American Shoulder and Elbow Surgeons (ASES) score at the final follow-up.

Patients who underwent surgical intervention had significantly greater deficits at baseline on external rotation and internal rotation testing than did those who did not undergo surgery. The participants responded favorably to treatment, with improvements in range of motion including forward elevation ( $p < 0.0001$ ), external rotation ( $p < 0.0001$ ) and internal rotation ( $p < 0.0001$ ). Only five shoulders demonstrated decreased range of motion in one or more plane. Range of motion gains were greater in patients who underwent surgery than among those who underwent nonoperative treatment ( $p < 0.05$  for all comparisons). Comparison of the nonoperative and operative treatment groups revealed that SST and ASES scores at final follow-up were similar for both groups.

**Conclusion:** This study of patients with adhesive capsulitis demonstrates that a nonoperative treatment program is effective for most patients, and that, for nonresponders, manipulation and arthroscopic release can produce good results.

Riill, B., et al. Predictors of Outcome after Nonoperative and Operative Treatment of Adhesive Capsulitis. *Am J Sports Med.* 2011, March; 39(3): 567-574.

### **DONOR KNEE RECOVERY AFTER AUTOLOGOUS OSTEOCHONDRAL TRANSPLANTATION**

Autologous osteochondral transplantation is an established surgical intervention for osteochondritis desiccans (OCD) of the humeral capitellum. This disorder most commonly affects throwing athletes in their early teens. The goal of the procedure is to prevent elbow osteoarthritis and allow return to previous activity levels. Only a few studies have examined morbidity at the harvest site in the knee. This prospective study assessed the outcomes of donor knee sites after this procedure.

Twelve male throwing athletes with severe OCD of the humeral head underwent osteochondral transplantation, with cells harvested from the contralateral knee. The

patients were followed for 24 months, with assessments including pain, the presence of joint effusion, radiographic changes, muscle strength and Lysholm scores.

At three months post-surgery, 10 of the 12 patients were pain free, with 100 point Lysholm scores and no joint effusions. Knee extensor muscle power was reduced at three-month follow-up, with 11 of the 12 athletes recovering full strength at one year. Radiographic analysis found no evidence of osteoarthritis at two-year follow-up.

**Conclusion:** This study of athletes undergoing autologous transplantation for osteochondritis desiccans found a decrease in knee extensor strength in the donor knee at three months, but no long-lasting effects at 12 months.

Nishimura, A., et al. Functional Recovery of the Donor Knee after Autologous Osteochondral Transplantation for Capitellar Osteochondritis Dessecans. *Am J Sports Med.* 2011, April; 39(4): 838-842.

### **COMBINING CYTOKINE INHIBITORS FOR NUCLEUS PULPOSUS INDUCED NERVE INJURY**

Accumulating experimental evidence indicates that sciatica due to disc herniation and low back pain may relate to activation and sensitization of intraspinal structures by substances within the intervertebral discs. While tumor necrosis factor is often considered to be a significant factor in inflammatory events, this factor also acts through other pro-inflammatory cytokines. This study was designed to determine whether combining cytokine inhibitors produces additive effects, as compared to separate applications.

This animal study included 15 pigs undergoing nucleus pulposus harvesting, with this content applied to the sacro-coccygeal cauda equina. In five subjects, the nucleus pulposus was mixed with 100 mcg of anti-tumor necrosis factor alpha antibody (anti-TNF $\alpha$  antibody). In another five, the nucleus pulposus was mixed with 100 mcg of anti-interleukin-one beta antibody (anti-IL-1B). In the remaining five, the nucleus pulposus was mixed with both. Seven days after the application, an electrodiagnostic

study was completed on each animal by an electrodiagnostician held blind to the treatment group.

Application of anti-IL-1B did not significantly reduce the effects of the nucleus pulposus. The addition of anti-TNF $\alpha$  antibody was more efficacious, although that intervention only partially reduced the effects ( $p=0.0788$ ). The combined antibodies improved nerve conduction losses significantly more than did either intervention alone ( $p=0.0442$  and  $p=0.001$ , respectively).

**Conclusion:** This animal study of nucleus pulposus induced nerve injury found that combining two cytokine inhibitors reduces nerve damage more than does either inhibitor individually.

Olmaker, K., et al. Combination of Two Cytokine Inhibitors Reduces Nucleus Pulposus Induced Nerve Injury More than Using Each Inhibitor Separately. *Open Ortho J.* 2011; 5: 151-153.

#### **ROBOTIC ANKLE TRAINING FOR GAIT AFTER STROKE**

Among new approaches for the treatment of hemiparesis after stroke, robotics technology has most often focused on arm function. Studies of robotics for lower extremity function have produced mixed results. This study investigated the utility of an ankle robotic intervention for the treatment of hemiparetic gait in chronic stroke survivors.

Eight patients with chronic stroke and residual hemiparetic gait deficits were recruited. All underwent training sessions three times per week for six weeks. At each treatment, an ankle robot was attached to a modified orthopedic shoe, with the patient asked to produce dorsiflexion or plantar flexion movements in response to a video game display. Each session involved 560 repetitions. The participants were assessed at the beginning and at the completion of training, using clinical and robot-based measures to evaluate ankle impairment and gait function.

Treatment resulted in increased targeting accuracy, speed, and smoothness of unassisted movements in the dorsiflexion-plantarflexion range during unassisted movements. The mean, active range of motion in plantarflexion increased in six of the

eight subjects ( $p<0.05$ ), with increases in dorsiflexion that failed to reach significance. Subjects significantly increased self-selected walking speed over the six-week period of training through a combination of longer stride lengths and faster cadence.

**Conclusion:** This study of patients with hemiparesis due to stroke found that use of a modular impedance controlled ankle robot improved ankle motor control and resulted in improved walking speed.

Forrester, L., et al. Ankle Training with a Robotic Device Improves Hemiparetic Gait after a Stroke. *Neurorehab Neural Repair.* 2011, May; 25(4): 369-377.

#### **ANTIDEPRESSANT MEDICATIONS FOR DEPRESSION WITH DEMENTIA**

Depression is common among people with dementia. Depression not only adds to the morbidity and mortality of this population, but is also associated with greater functional impairment. This meta-analysis evaluated the efficacy of antidepressant medication in people with depression and dementia.

Medline and the Cochrane Trials Registry were searched for articles published between 1966 and 2010. Information extracted included diagnostic criteria for depression and dementia, medication dosing method, treatment duration, depression rating scores, clinical outcome and dropout rate. Response was defined as a 50% improvement on the Hamilton Depression Rating Scale, the Montgomery Asberg Depression Rating Scale or the Cornell Scale for Depression in Dementia, or was defined as being "much" or "very much" improved on a global assessment scale.

The Medline search identified 47 studies and the search of the Cochrane database identified an additional 64. Of those, only seven trials met the selection criteria, with these including 330 participants. The quality of the trials ranged from good to excellent. Two of the studies found antidepressants to be more effective than placebo, while five others did not. The meta-analysis of response rates in six trials demonstrated significant variability among the studies.

**Conclusion:** This meta-analysis of antidepressant medications for treatment of depression among patients with dementia found a trend toward efficacy, without reaching statistical significance.

Nelson, J., et al. A Systematic Review and Meta-Analysis of Placebo-Controlled Antidepressant Studies in People with Depression and Dementia. *JAGS.* April; 59(4): 577-585.

#### **ROLE OF STEROIDS IN SEVERE TRAUMA**

The overall rate of posttraumatic pneumonia has been estimated to be between 40% and 60%, occurring primarily in patients with traumatic brain injury. Thus, prevention of posttraumatic pneumonia is a major clinical and economic issue. Stress dose hydrocortisone has been suggested as a means of improving outcome in septic patients with critical illness related corticosteroid insufficiency. This multi-center, randomized, double-blind, placebo-controlled study explored whether stress dose levels of hydrocortisone can diminish the prevalence of hospital acquired pneumonia in patients hospitalized for trauma.

This trial included patients with multiple trauma, all of whom were older than 15 years of age and expected to require mechanical ventilation for more than 48 hours. The subjects were randomly assigned either to receive hydrocortisone at 200 mg per day for five days, tapering over the next two days, or to receive a placebo. The primary outcome measure was the occurrence of hospital acquired pneumonia within 28 days of randomization. Secondary outcomes included duration of mechanical ventilation and of intensive care unit stay and rates of death, other infections and organ failures, as well as duration of vasopressor support on day 28.

Of the participants in the treatment group, 35.6% developed pneumonia, compared with 51.3% in the placebo group ( $p<0.07$ ). Mechanical ventilation-free days were increased by approximately four days among the group receiving steroids ( $p<0.001$ ). A significantly greater reduction in mortality was realized in the treatment group as compared to the control group ( $p=0.02$ ).

**Conclusion:** This study of patients hospitalized for trauma suggests that a short duration, high dose of hydrocortisone decreases the risk of hospital acquired pneumonia and reduces the duration of ventilation.

Roquilly, A., et al. Hydrocortisone Therapy for Patients with Multi-Trauma. **JAMA**. 2011, March 23/30; 305(12): 1201-1209.

### **SINGLE FIBER CONDUCTION LOSS ALLOWS EARLY DIAGNOSIS OF DIABETIC POLYNEUROPATHY**

Polyneuropathy is the most common neurological complication of diabetes mellitus. Early diagnosis plays a key role in appropriate clinical management for the prevention of diabetic complications. Nerve conduction velocity is the most common and reliable method to assess myelin nerve dysfunction. However, conventional conduction velocity studies, using surface electrodes, reflect only the fastest conducting nerve fibers of the alpha motor axon population. This technique's application in the evaluation of early stage disease is very limited. However, single fiber evaluation allows the detection of early, mild or partial, myelin damage when conventional tests are still normal. This study was designed to determine whether single fiber conduction velocity can improve detection of mild motor nerve function abnormalities in the early stages of diabetic polyneuropathy.

Twenty-one patients with hemoglobin A-1 C levels of less than eight percent and fasting blood glucose levels of less than 140 mg/dl were studied. All patients underwent physical examination. No subject had a clear clinical picture of polyneuropathy. However, nine had transient, asymmetric, neuropathic symptoms suggestive of mild, early nerve impairment. For each patient, single fiber conduction velocity and conventional conduction velocity results were recorded. These findings were compared to that subject's neuropathic symptoms.

Conventional conduction studies demonstrated abnormal findings in three patients, with single fiber results demonstrating abnormalities in three additional patients. Symptoms reported by the patients were

associated with abnormal single fiber, but not conventional, conduction velocities.

**Conclusion:** This pilot study found that single fiber conduction velocity is more sensitive than is conventional conduction velocity in detecting mild myelin damage at the early stages of diabetic polyneuropathy.

Padua, L., et al. Single Fiber Conduction Velocity Test Allows Earlier Detection of Abnormalities in Diabetes. **Musc Nerve**. 2011, May; 43: 652-656.

### **TAI CHI FOR CHRONIC HEART FAILURE**

Historically, patients with chronic systolic heart failure have been considered too frail to exercise. However, data from trials involving patients with heart failure during the prior 15 years have reported specific, and sometimes profound, pathophysiologic improvements through different exercise regimens. While tai chi has proven to be a successful exercise option for other groups of patients, its efficacy for patients with heart failure has not yet been clearly demonstrated.

This study included 100 patients from ambulatory clinics at three academic medical centers. The subjects were randomly assigned to participate in either a 12-week tai chi exercise program or a heart health education program. All participants continued to receive usual care, which included pharmacologic therapy and general exercise advice. The tai chi intervention consisted of one-hour group classes, held twice weekly for 12 weeks. The protocol included traditional warm-up exercises and five, subsequent, simplified tai chi movements.

The patients were encouraged to practice at home at least three times per week. Participants in the control group underwent education sessions at the same duration and frequency as the tai chi group. Outcome measures were obtained at baseline and at 12 weeks, and included exercise capacity and disease specific quality of life.

The subjects' mean age was 67 years, with a mean baseline left ventricular ejection fraction of 29% and a median New York Heart Association heart failure classification of II. At 12-week follow-up, no

significant differences were seen between the groups on the six-minute walk test or in peak oxygen uptake. However, those in the tai chi group improved significantly more in quality of life than did controls.

**Conclusion:** This study of patients with chronic heart failure found that tai chi exercise can improve quality of life, mood and exercise self-efficacy to a greater extent than education alone.

Yeh, G., et al. Tai Chi Exercise in Patients with Chronic Heart Failure. **Arch Intern Med**. 2011, April 25; 1 (8): 750-757.

### **CHOLESTEROL MANAGEMENT IN THE UNITED STATES**

The third report of the National Cholesterol Education Program Adult Treatment Panel provides guidelines for the detection, evaluation and treatment of high blood cholesterol in adults through lifestyle modification and drug therapy. This study sought to assess the prevalence of having ever had one's blood tested for cholesterol levels, to determine the proportion currently following recommended practices for managing cholesterol and to evaluate the association between serum cholesterol levels and cholesterol management practices.

The NHANES 1996-2006 is a complex, multistage, area probability sample representation of the United States non-institutionalized civilian population. The overall survey sample included 50,939 persons, among whom 39,352 were interviewed and examined. Information concerning cholesterol management practices was obtained from survey questions. Cholesterol management was examined among adults previously diagnosed with high cholesterol (n=4,753) who were advised to change their lifestyles through low-fat diets, weight loss, exercise and/or medications. A serum total cholesterol of greater than 240 mg/dL was defined as high, levels of 200 to 240 mg/dL were defined as borderline and levels of less than 200 mg/dL were defined as desirable.

Seventy percent of adults 20 years of age or older reported having undergone at least one blood cholesterol test in their lifetime. Among those, 57% reported having been tested within the previous year.

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\*Thiru Annaswamy, M.D.  
Taras Ploskanych, M.D.  
Tong Zhu, M.D.  
UT SW Medical Center, Dallas TX

\*Daniel Herman, M.D., Ph.D.  
UVA, Charlottesville, VA

\*Elaine Tsao, M.D.  
Andrew C. Hsu, M.D.  
University of Washington, Seattle, WA

\*Bonnie Weigert, M.D.  
\*Walton Schalick, III, M.D., Ph.D.  
University of Wisconsin, Madison, WI

\*William Carter, M.D.  
\*Steven Jackson, M.D.  
VCU, Richmond, VA

\*Jon Kronberg, M.D.  
Vijay Katukuri, M.D.  
Washington University, St. Louis, MO

**Executive Editor Emeritus**  
Donald F. Langenbeck, Jr., M.D.

**Subscription Manager**  
Michael P. Burke, M.S.

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Of those diagnosed with high cholesterol by a healthcare professional, 89% were advised to follow a lifestyle change plan or take a prescribed medication. Among that group, 69% to 80% followed the advice. After adjusting for age, gender, education and race, adults on medication only, as well as those practicing a combination of lifestyle changes and taking medication, were significantly more likely to have a cholesterol level of below 240 mg/dL than were those making lifestyle changes only. More than 30% of subjects who reported that they had been told that they had high blood cholesterol had current serum total cholesterol levels of 240 mg/dL or more.

**Conclusion:** This study demonstrates that combining medication and lifestyle changes is more strongly associated with decreasing cholesterol than is making one or more lifestyle changes without medication.

Yoon, S., et al. Cholesterol Management in the United States: The National Health and Nutrition Examination Survey: 1996 to 2006. *Ann Epidem* 2011, May; 21(5): 318-326.

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