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## SPA THERAPY AND OSTEOARTHRITIC KNEE PAIN

Although not popularly prescribed in the United States, spa therapy is frequently used in Europe for knee osteoarthritis (OA). To date, high-quality studies have not been conducted to demonstrate the efficacy of this treatment. This study investigated whether spa therapy plus home exercises and usual medical treatment provide any benefit over exercise and usual treatment for the management of knee OA.

This randomized, controlled trial included 451 subjects studied between June of 2006 and April of 2007. Of those, 223 were randomized to home exercise and continuation of their usual treatments of medication or physical therapy. The other 222 patients received 18 sessions at one of the three largest spa resorts in France. Therapies included mineral hydrogel, manual massages of the knee and thigh, as well as mud and pool sessions. At one, three, six and nine months, the subjects self-assessed their pain. The primary endpoint was the achievement of minimal clinically important improvement (MCII), as defined by a significant change on the scales, as well as an absence of surgery at six months.

At six months, 36.4% of the control group and 50.8% of the spa therapy group achieved MCII ( $p=0.005$ ). At nine months, 35.8% of the control group and 53.8% of the spa therapy group achieved MCII. At six months, 29.7% of the control group and 54.4% of the spa therapy group stated that their knee pain was better after treatment ( $p<0.001$ ).

**Conclusion:** This randomized, controlled trial comparing spa therapy with usual treatment found that a three-week course of intensive spa therapy is effective in reducing pain in patients with knee osteoarthritis.

Forestier, R., et al. Spa Therapy in the Treatment of Knee Arthritis: A Large, Randomized, Multi-Center Trial. *Ann Rheum Dis.* 2010, April; 69(4): 660-665.

## LEG LENGTH DISCREPANCY AND RISK OF KNEE ARTHRITIS

Leg length inequality (LLI) occurs in 70% of the population. Trauma or developmental abnormalities are frequent causes. LLI may play a role in low back pain, osteoarthritis (OA) of the hip and knee, trochanteric bursitis and running injuries. This study sought to determine whether LLI is associated with the development of knee OA.

This multi-center, longitudinal, community-based study included 3,026 participants ranging in age from 50 to 79 years. All participants had knee OA or a high risk for knee OA due to knee pain, obesity, knee injury or knee surgery. At baseline, data collected included demographic information, full limb radiographs and standard knee radiographs. Participants were assessed at a 30-month follow-up visit. Trained technologists measured leg length using limb radiography. Knee OA was defined by radiologic criteria. Outcome measures included prevalent, incident and progressive OA of the knee over the 30 months of the study.

A LLI of 1 cm or more was observed in 14.5% of the participants at baseline. A LLI of at least 1 cm was associated with greater incident radiographic and symptomatic OA in the shorter leg as compared to those with a discrepancy of less than 1 cm. An inequality of as little as 0.5 to 1 cm increased the risk for prevalent knee OA, primarily in the shorter leg ( $p < 0.001$ ). Also a LLI of 1 cm or more was associated with increased odds of progression in the shorter leg over 30 months of follow-up, as compared

with an inequality of less than 1 cm (Odds Ratio, 1.3).

**Conclusion:** This study found that a leg length inequality of at least 1 cm is associated with prevalent, incident, symptomatic and progressive osteoarthritis of the knee, especially in the shorter leg.

Harvey, W., et al. Association of Leg Length Inequality with Knee Osteoarthritis. *Ann Int Med.* 2010, March 2; 152: 287-295.

## ADVERSE EFFECTS OF TOPICAL NSAIDS IN OLDER ADULTS WITH OSTEOARTHRITIS

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of osteoarthritis (OA) in older adults. Although the safety of topical NSAIDs in older adults with OA has not been well studied, these agents have been employed in the United States as a presumably safe alternative to oral NSAIDs. This literature review evaluated the safety of these topical agents.

A systematic search of MEDLINE, Scopus, Web of Science, Cochrane databases, dissertation abstracts and American College of Rheumatology meeting abstracts was performed to identify studies reporting on adverse events among patients receiving topical NSAIDs. A total of 953 such articles were identified. Sixteen of those were randomized, controlled trials.

In those 16 studies, a total of 4,428 subjects were randomized. Fourteen of the 16 trials studied OA of the knee. Up to 39.3% of the subjects reported adverse effects at the site of application, with dry skin the most common. Up to 17.5% of the topical users reported systemic side effects, with the most common of those being headaches, followed by abdominal distress in up to 15%. The withdrawal rate due to adverse

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events with topical agents was comparable to that of oral agents.

**Conclusion:** This systematic review of the literature found that, while topical NSAIDs are safer for the treatment of osteoarthritis than are oral NSAIDs, a substantial portion of older adults report systemic adverse effects.

Makris, U., et al. Adverse Effects of Topical Nonsteroidal Antiinflammatory Drugs in Older Adults with Osteoarthritis: A Systematic Literature Review. *J Rheum.* 2010, April; Doi:10.3899/jrheum.090935.

### **ANTICONVULSANT MEDICATIONS AND THE RISK OF SUICIDE**

In 2008, the U.S. Food and Drug Administration (FDA) found that patients taking anticonvulsant drugs had approximately twice the risk of suicidal behavior or ideation than those receiving a placebo. This study evaluated the increased risk of attempted or completed suicide and combined suicidal acts or violent death associated with these medications.

All subjects had made medical and pharmacy claims recorded in the HealthCore Integrated Research Database (HIRD). Participants in this study were 15 years of age or older who had begun taking anticonvulsant medication between July of 2001 and December of 2006. The subjects were followed for 180 days, until drug discontinuation or switching, for the occurrence of the study outcome. Identified suicide attempts were documented through emergency department visits and hospitalizations.

A total of 297,620 new treatment episodes of anticonvulsant medications were identified. The most frequently prescribed medications were gabapentin (48%) and topiramate (19.4%). The mean follow-up time for anticonvulsant medications was 91 days, and the median was 60 days. During the study, there were 827 attempted or completed suicides, for a total of 868 combined events within 180 days of initiation of any anticonvulsant medication. The data were assessed to evaluate all outcomes in 180 days among users of all anticonvulsant medications compared with new users of topiramate.

The risk for all outcomes was increased more for gabapentin, lamotrigine, oxcarbazepine, tiagabine and valproate than for topiramate. The risk of attempted or completed suicide was meaningfully increased for gabapentin (hazard ratio (HR) 1.42), lamotrigine (HR, 1.84), oxcarbazepine (HR, 2.07), tiagabine (HR, 2.41) and valproate (HR, 1.65). The risk remained increased for gabapentin in subgroups of younger and older patients, patients with mood disorder, and patients with epilepsy or seizure disorders.

**Conclusion:** This study found that the use of gabapentin, lamotrigine, oxcarbazepine and tiagabine is associated with an increased risk of suicidal acts or violent deaths to a greater extent than is the use of topiramate.

Paterno, E., et al. Anticonvulsant Medications and Other Risk of Suicide, Attempted Suicide or Violent Death. *JAMA.* 2010, April 14; 303 (14): 1401-1409.

### **COMPARISON OF 10 ANTI-EPILEPTIC DRUGS IN OLDER ADULTS WITH EPILEPSY**

The management of epilepsy in elderly patients can be complicated by many factors. Some of the new antiepileptic drugs (AEDs) have claimed a more favorable adverse effect profile, with reduced pharmacokinetic interactions, for the elderly. However, few studies have compared the effectiveness of different AEDs in the elderly. This study evaluated the effectiveness of 10 AEDs for their ability to reduce seizures and for their tolerability among older adults with epilepsy.

This retrospective review included all 417 patients, ages 55 years or older, seen in an outpatient comprehensive epilepsy center during a five-year period. Two hundred ninety-three of these patients had been newly started on AEDs during this period. Only the 10 most common AEDs were included in the analysis. The main outcome measure was the percentage of patients who remained taking any particular AED for at least 12 months. In addition, efficacy was determined as 12 months of freedom from seizures.

Overall, 329 of 417 patients continued taking at least one AED for

at least one year. Of the 247 patients newly started on any AED, the average 12-month retention rate was 65%. The highest retention rate was seen among those taking lamotrigine (78.6%), higher than the 12-month retention rates seen with carbamazepine, gabapentin, oxcarbazepine, phenytoin and topiramate ( $p < 0.05$ ). The second highest retention rate occurred for levetiracetam (72.5%), and was significantly higher than with carbamazepine and oxcarbazepine. Oxcarbazepine had the worst retention rate, significantly lower than those of all of the other AED's. Without controlling for severity, lamotrigine had the highest 12-month seizure freedom rate (54.1%), followed by levetiracetam (42.6%).

**Conclusion:** This retrospective study of older adults with epilepsy found that, among the 10 most commonly prescribed seizure medications, lamotrigine was the most effective for reducing the rate of seizures.

Arif, H., et al. Comparative Effectiveness of 10 Antiepileptic Drugs in Older Adults with Epilepsy. *Arch Neur.* 2010, April; 67(4): 408-415.

### ADVERSE EFFECTS OF ANTIEPILEPTIC DRUGS

Epilepsy, characterized by recurrent, unprovoked seizures, can in most patients be successfully treated by mono or poly therapy. Traditional antiepileptic drugs (AEDs), including carbamazepine, phenytoin and valproate, are considered to be first-line treatments for epilepsy in both the United States and Europe. Valproate has been considered the treatment of choice for generalized, tonic-clonic seizures. Despite treatment with AEDs, approximately 40 to 50% of people with epilepsy continue to experience seizures or experience intolerable medication side effects. This study evaluated the adverse effects of four commonly prescribed AEDs in an adult, Chinese sample with epilepsy.

This study included adult patients ranging in age from 16 to 70 years, all with newly diagnosed active epilepsy. Those subjects were recruited from January 2000 to January 2005, with follow-up for 24 months. The investigator selected monotherapies,

including carbamazepine at 300 to 600 mg daily, phenytoin at 300 to 500mg daily, valproate at 600 to 1200 mg daily and lamotrigine at 100 to 200 mg daily. The medications were administered based upon seizure type by the primary treating physicians and two epileptologists. The doctors were permitted to increase or decrease drug doses depending upon the level of seizure control, seizure type and adverse side effects. The patients were followed at two-week intervals during the first two months, at three month intervals for the remainder of the first year and then every six months for the second year. The patients were asked to keep a daily seizure diary and to report adverse effects.

At the end of two years, 62.6% of the 505 subjects had completed the monotherapy study. Due to incomplete seizure control or adverse side effects, medications were changed in 37.4% of the patients. These subjects included 35.7% of those initiated on carbamazepine, 44.1% of those initiated on phenytoin, 38.5% of those initiated on valproate and 33.7% of those initiated on lamotrigine.

The most common reason for discontinuation of monotherapy was unsatisfactory seizure control, which occurred in 33%, 39%, 37% and 29.1%, respectively, of those initially treated with carbamazepine, phenytoin, valproate and lamotrigine. Overall, 18% of the patients experienced side effects, including 14.9% of those on carbamazepine, 30.5% of those on phenytoin, 16.7% of those on valproate and 18.6% of those on lamotrigine. The data indicated that adverse events, while frequent, were not severe, and were not the main reason for withdrawal from the study.

**Conclusion:** This study of adult, Chinese patients treated for new onset epilepsy found that approximately 35% of those treated with common anti-seizure medications switched to or added other medications due to unsatisfactory results. A total of 18% experienced adverse side effects, ranging from 15% for carbamazepine to 31% for phenytoin.

Zeng, K., et al. Adverse Effects of Carbamazepine, Phenytoin, Valproate and Lamotrigine Monotherapy in Epileptic Adult Chinese Patients. *Clin Neur*

*Neurosurg.* 2010, May; 112: 291-295.

### ICE SLURRY INGESTION FOR COMPETITION IN HOT ENVIRONMENTS

Increased core body temperature associated with exercise in hot environments is generally thought to be the major factor causing fatigue and reduced motor output during prolonged exercise in the heat. It is believed that pre-cooling may be a useful strategy for combating the effect of heat stress on exercise performance. This study examined the effects of ice slurry versus cold water ingestion on thermoregulatory responses and prolonged submaximal exercise performance in the heat.

The study's sample comprised ten, healthy, male volunteers who were considered moderately active, were participating in recreational sport and had no previous history of heat illness or injury. Multiple laboratory and body measurements were obtained before and after exercise. These included oxygen uptake and ventilatory threshold during progressive exercise testing. The subjects maintained a normal lifestyle, with adequate nutrition and hydration during the study, while avoiding supplementation and strenuous exercise. The participants were alternated between two separate treadmill running trials in hot conditions after ingesting ice slurry or cold water. During the exercise protocols, skin and rectal temperatures were recorded. In addition, heart rate, pulmonary function, hydration status, sweat rate and time to exhaustion were recorded.

During the drinking period, the mean, ambient temperature was similar between trials. On average, the subjects ran for a longer period of time after the ice slurry (50.2 minutes) than cold water (40.7 minutes), a mean running time increase of 9.5 minutes ( $p = 0.001$ ). Before running, rectal temperatures dropped more after ice slurry ingestion than cold water, and remained lower for the first 30 minutes of exercise ( $p = 0.001$ ). At exhaustion, rectal temperature was higher in the ice slurry condition ( $p = 0.001$ ). During exercise, there was no significant difference between the

groups in mean skin temperature, heart rate or sweat rate.

**Conclusion:** This study found that using an ice slurry as a pre-cooling maneuver can delay the time to reach critically high core temperatures and, in turn, improve exercise performance in recreational athletes who exercise in hot environments.

Siegel, R., et al. Ice Slurry Ingestion Increases Core Temperature Capacity and Running Time in the Heat. *Med. Sci in Sp Exer.* 2010, April; 42(4): 717-725.

### EPIDEMIOLOGY OF SHOULDER DISLOCATIONS IN THE UNITED STATES

The incidence of shoulder dislocation in the United States population has been estimated, but not accurately determined, by previous studies. This cross-sectional study aimed to better determine the incidence and demographic risk factors of shoulder dislocation in the United States.

This cross-sectional, descriptive, epidemiologic study utilized cases of shoulder dislocation recorded in the consumer product safety commission's national electronic injury surveillance (NEISS) database. This database samples 100 hospitals which were originally designated by stratified, randomized sampling of all United States hospitals with emergency departments. This stratification was based on both geographic location and emergency department volume data. From these data, dislocations from 2002 through 2006 were queried to determine total numbers of dislocations and injury characteristics. Rates were calculated using United States Census data.

A total of 8,940 shoulder dislocations were identified. Overall, 46.8% of all dislocations were seen in patients between 15 and 29 years of age. The highest number of dislocations occurred at 16.5 years of age. The incidence in the United States was estimated to be 23.9 per 100,000 persons. Of the total shoulder dislocations, 72% occurred in males. Dislocations most frequently resulted from falls (58.8%), occurring at home (47.7%) or at sites of sports/recreation (34.5%).

**Conclusion:** This national study of shoulder dislocations in the United

States suggests that the incidence is 23.9 per 100,000 person years. This finding is twice the value estimated by previous studies.

Zachilli, M., et al. Epidemiology of Shoulder Dislocations Presenting to Emergency Departments in the United States. *J Bone Joint Surg.* 2010, March; 92: 542-549.

### COLLEGE FOOTBALL INJURIES AND FIELD SURFACE

In college football, numerous injuries have been attributed to playing on artificial turf. Recently, FieldTurf was developed to duplicate the playing characteristics of natural grass. No long-term studies have previously compared game related collegiate football injuries between these two surfaces. This study sought to quantify the incidence, mechanisms and severity of game related collegiate football injuries, comparing the two surfaces.

Twenty-four universities classified as division I by the National Collegiate Athletic Association were used in this study of game-related football injuries sustained on FieldTurf versus actual grass during a three year period. The study began with 11 universities and added 13 in year two, using a total of 465 seasonal games played on either FieldTurf (n=230) or natural grass (n=235). All players underwent a pre-participation physical examination under the care of a team physician. Injuries were recorded throughout the season, and were compared by playing surface.

A total of 2,253 injuries were documented. Of those, 46.6% were sustained while playing on FieldTurf and 53.4% while playing on natural grass (p=0.016). Further, when substantial injuries were compared between types of playing surfaces, significantly fewer injuries were noted among those playing on FieldTurf than on natural grass (p=0.02).

**Conclusion:** This study of college football players found that, when competing on FieldTurf, athletes incurred fewer injuries, as well as fewer serious injuries, than when playing on natural grass.

Myers, M. Incidence, Mechanisms and Severity of Game Related College Football Injuries on FieldTurf

versus Natural Grass. *Am J Sp Med.* 2010, April; 38: 687-697.

### MOTOR FUNCTION AND INDEPENDENCE AFTER SUBTHALAMIC STIMULATION IN PARKINSON'S DISEASE

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor, sensory, autonomic, cognitive, behavioral and sleep related symptoms. Dopaminergic medications used in PD can be effective, although the effects may not be sustained. Deep brain stimulation (DBS) has grown in favor as a treatment. The results of treatment when targeting the subthalamic nucleus (STN) have not been well documented. In addition, previous studies have not looked specifically at health related quality of life. This study sought to provide pilot data regarding outcomes following STN DBS, using the questions on a life satisfaction questionnaire.

Twenty-one subjects with PD underwent STN DBS, all performed by the same neurosurgeon. The subjects completed health-related quality of life questionnaires, specifically designed for the DBS population, at baseline and at six and 12 months postoperatively. Additional assessments included the Geriatric Depression Scale (GDS), the Unified Parkinson's Disease Rating Scale (UPDRS), the Lang-Fahn Activities of Daily Living Dyskinesia Scale (LFADLDS), Modified Hoehn and Yahr scores, the Folstein Mini-Mental Status Examination (MMSE) and the EQ-5D.

After DBS, significant improvements were noted in general health satisfaction (p=0.03) and in movement disorder specific health satisfaction (p=0.007). However, there was no significant change in general life satisfaction. Further, there was no significant worsening of any aspect of health related quality of life or patient satisfaction. Following DBS, patients reduced dopaminergic therapy by an average of 499 LEU mg/day. No significant change was seen in postoperative MMSE or Geriatric Depression Scale scores. No patient experienced serious or persistent complications related to DBS, and none required a DBS revision.

**Conclusion:** This study found that deep brain stimulation to the subthalamic nucleus may be a reasonable option for patients with Parkinson's disease, with some improvement in satisfaction with motor function, independence and general health. However, overall quality of life scores did not change among the patients in this study.

Ferrara, J., et al. Motor Function and Independence Improved after Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease. *J Neur Neurosurg Psych.* 2010, March 81(3): 315-319.

### DACLIZUMAB IN ACTIVE RELAPSING MULTIPLE SCLEROSIS

Daclizumab is a recombinant humanized monoclonal antibody specific for the alpha subunit (CD 25) of the human-high infinity interleukin two receptor. CD 25 is expressed at low levels on resting T cells and is rapidly upregulated after T cell activation. CD 25 activity has been implicated in autoimmunity, with studies of CD 25 antagonism demonstrating expansion of a regulatory subset of natural killer cells (CD 56). Previous, nonrandomized studies have suggested that daclizumab can benefit patients with multiple sclerosis (MS). This study sought to determine the effect of adding daclizumab for patients with relapsing MS who have disease activity despite ongoing use of interferon beta.

This study included patients, 18 to 55 years of age and diagnosed with MS, who had been on a stable interferon beta regimen for six months or more. The subjects were randomly assigned to receive interferon beta plus one of three supplemental treatments. These included daclizumab at 2 mg per kilogram every two weeks, daclizumab at 1 mg per kilogram every four weeks or placebo for 24 weeks. The primary endpoint was the total number of new or enlarged gadolinium contrast enhanced lesions detected on brain MRI studies. The scans were completed every four weeks between weeks eight and 24. Secondary endpoints, measured at week 24, were changes in the number and volume of lesions on T1 and T2 weighted MRI.

The adjusted mean number of new or enlarged gadolinium contrast-enhancing lesions was 4.75 in the interferon beta and placebo group, compared with 1.32 in the interferon beta and high-dose daclizumab group ( $p=0.004$ ) and 3.58 in the interferon beta and low-dose daclizumab group ( $p=0.51$ ). Daclizumab was not associated with significant changes in the absolute number of T cells, B cells, or natural killer cells. The number of CD 56 natural killer cells was seven to eight times higher in both daclizumab groups than with placebo ( $p=0.002$ , and  $p<0.0001$ , respectively).

**Conclusion:** This study of patients receiving beta interferon for active relapsing multiple sclerosis found that treatment with 2 mg per kilogram of daclizumab every two weeks reduced the number of new or enlarged central nervous system lesions.

Wynn, D., et al. Daclizumab in Active Relapsing Multiple Sclerosis (Choice Study): A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Add On Trial with Interferon Beta. *Lancet Neur.* 2010, April; 9:381-390.

### RILUZOLE FOR CEREBELLAR ATAXIA

Hyperexcitability of the deep cerebellar nuclei is thought to underlie different forms of cerebellar ataxia. Riluzole opens small conductance calcium activated potassium channels which have been shown to exert a critical regulatory effect on the firing rate of neurons in deep cerebellar nuclei. This study sought to determine whether riluzole might be effective for symptomatic relief of cerebellar ataxia.

This double-blind, placebo-controlled, pilot study randomized 38 patients with chronic cerebellar ataxia with varied patterns of etiology, duration and disability duration. The patients received either riluzole at 100 mg per day or a placebo. Outcome measures, including scores on the international cooperative ataxia rating scale (ICARS), were obtained at baseline and at four and eight weeks. Subsets of the ICARS were reviewed for further analysis. Patients with a five-point improvement in ICARS scores were assessed across time points and between groups.

After four weeks, nine of 19 riluzole patients and one of 19 placebo subjects obtained a five-point or more improvement in ICARS score. The difference between the groups became highly significant after eight weeks (odds ratio=39). The absolute difference at eight weeks was 63.2%. The riluzole group demonstrated greater improvement than the placebo group on both total scores and three subscores, including static function, kinetic function and dysarthria ( $p<0.001$  for all). Cerebellar ataxia deteriorated during the study period in only two patients, both of whom received the placebo.

**Conclusion:** This study of patients with cerebellar ataxia found that riluzole may be effective for symptomatic improvement, including static and kinetic function as well as dysarthria.

Ristori, G., et al. Riluzole in Cerebellar Ataxia: A Randomized, Double-Blind, Placebo-Controlled Pilot Trial. *Neur.* 2010, March 9; 74 (10): 839-845.

### SINGLE PULSE TRANSCRANIAL MAGNETIC STIMULATION FOR MIGRAINE

Migraine is a primary headache disorder affecting 18% of women and six percent of men in the United States and Western Europe. The two major forms include migraine without aura and migraine with aura. Migraine with aura affects approximately 20 to 30% of patients. The presumed substrate of migraine with aura is cortical spreading depression, consisting of a wave of excitation followed by a wave of inhibition of both neurons and glia, which spreads across the cortical mantle. Work with animals has demonstrated that transcranial magnetic stimulation (TMS) disrupts this depression wave. This study assessed the efficacy and safety of a novel, portable, single-pulse TMS (sTMS) device for the acute treatment of migraine with aura.

This randomized, sham controlled, double-blind, parallel study included two phases and was conducted at 18 centers in the United States. Patients were eligible for participation if they were 18 to 70 years of age and met the International Classification of Headache Disorders criteria for migraine with aura. The subjects

were randomized to receive either tSMS or a sham treatment.

In phase I, the participants were asked to keep a headache diary for one month. In phase II, they were stimulated using a portable monophasic machine that delivered two pulses, 30 seconds apart, at an area just below the occipital bone. The patients self-administered these treatments, and were instructed to begin the treatment as soon as possible after an aura began, and always within one hour of aura onset. The subjects recorded their response at 30 minutes and at one, two, 24 and 48 hours after treatment.

Of the 164 patients treated for at least one attack, pain-free response rates two hours after treatment were significantly higher in the TMS group (39%) than in the sham group (22%) ( $p=0.0179$ ). More treatment patients achieved the sustained pain-free secondary outcome at 24 and 48 hours than did those receiving the sham treatment ( $p=0.04$  and  $p=0.03$ , respectively).

**Conclusion:** This randomized, blinded study found that single pulse transcranial magnetic stimulation is significantly more effective than sham stimulation for the treatment of migraine with aura.

Lipton, R., et al. Single Pulse Transcranial Magnetic Stimulation for Acute Treatment of Migraine with Aura: A Randomized, Double-Blind, Parallel Group, Sham Controlled Trial. *Lancet Neur.* 2010, April (9): 373-380.

### **DELIRIUM AFTER CORONARY ARTERY BYPASS GRAFT SURGERY**

Delirium after cardiac surgery has been reported for years. The presence of delirium after coronary artery bypass graft (CABG) surgery can be predicted in individuals who are older, male and have pre-existing cerebral disease, particularly dementia. This study sought to determine the role of postoperative delirium in the risk of late postoperative mortality among patients undergoing CABG.

All patients who underwent isolated, first time or redo CABG surgery at Johns Hopkins Hospital from January of 1997 through October of 2007 were included in the cardiac surgery database. On a daily

basis, surgical nurses identified possible cases of delirium. The charts and records of each individual were reviewed for the use of the word "delirium," with the majority of these cases discussed at the time of the event for clarification. Medical and demographic information was collected prospectively at the time of the surgery. The primary outcome variable for this study was all cause mortality.

Of the 5,121 individuals in the initial cohort, 5,034 were included in the final analysis. Of those, 304 individuals were identified with delirium and 4,748 without. Delirium was present in nine percent of individuals over the age of 65 and in three percent of those under the age of 65 ( $p<0.001$ ). The median survival time was 10.6 years for individuals with delirium and was beyond the range of the follow-up period for those without delirium ( $p<0.0001$ ). The death rate among those with delirium was 16.0 per 100 person-years, while that for those without delirium was 7.0 per 100 person-years ( $p<0.0001$ ). Postoperative length-of-stay was longer for individuals with delirium (15.3 days) than for those without delirium (7.3 days,  $p < 0.0001$ ).

**Conclusion:** This study of consecutive patients undergoing CABG found that delirium after surgery is a strong, independent predictor of mortality for up to 10 years post-surgery. This is especially true in younger individuals and those without a prior history of stroke.

Gottesman, R., et al. Delirium after Coronary Artery Bypass Graft Surgery and Late Mortality. *Ann Neur.* 2010, March; 67: 338-334.

### **DISABILITY IN THE LAST YEAR OF LIFE**

This study sought to identify clinically distinct trajectories of disability in the last year of life, and to determine whether the distribution of these trajectories differs according to the condition leading to death.

Participants were drawn from an ongoing, longitudinal study involving 754 community dwelling persons who were members of a large health plan. All subjects were 70 years of age or older and initially had no disability in the performance of activities of daily living, including bathing, dressing,

walking and transfers. Comprehensive, home-based assessments were completed at baseline and at 18-month intervals for 108 months. Information concerning the conditions leading to death was obtained from death certificates and by phone interviews with knowledgeable persons. The data were reviewed to determine the distribution of the disability trajectories for each of the conditions leading to death.

Five, distinct trajectories in the last year of life were identified: no disability, catastrophic disability, accelerated disability, progressive disability, and persistent, severe disability. The most common conditions leading to death were frailty, followed by organ failure, cancer, other causes, advanced dementia and sudden death. A predominant trajectory was observed only for advanced dementia (persistent severe disability) and sudden death (no disability). For the other four conditions, no more than 34% of the subjects followed any of the disability trajectories. Of these, dementia had the least variation and was characterized by high levels of disability throughout the last year of life. For the other five conditions, 27 to 80% of the subjects were not disabled or had very low levels of disability until a few months before death.

**Conclusion:** In this prospective cohort study of community dwelling older persons, five clinically distinct trajectories of disability were noted in the last year of life. For most, the course of disability at the end of life did not follow a predictable pattern based on the condition leading to death.

Gill, T., et al. Trajectories of Disability in the Last Year of Life. *New Eng J Med.* 2010, April 1; 362(13): 1173-1180.

### **BUPROPION AND COGNITIVE BEHAVIORAL THERAPY FOR WOMEN SMOKERS CONCERNED WITH WEIGHT GAIN**

Many women smokers have expressed concern about the weight gain that commonly accompanies an attempt to quit smoking cigarettes. Weight concerned smokers are less likely to intend to quit smoking. In addition, they are more likely to drop

out of treatment, have worse cessation outcomes, and gain more weight after cessation than do smokers without such weight concerns. In a previous study, the authors documented that cognitive behavioral therapy for smoking-related weight concerns can improve cessation rates. This study sought to determine whether combining such techniques with bupropion would enhance abstinence for weight concerned women smokers.

This randomized, double-blind, placebo-controlled trial was conducted between September of 1999 and October of 2005. Participants included 349 women smokers between the ages of 18 and 65 years who were smoking a minimum of 10 cigarettes per day and were motivated to quit. All had endorsed concern about post-cessation weight gain. The patients were randomized to receive either cognitive behavioral therapy for smoke related weight concerns (CONCERNS) or standard behavioral therapy aimed at smoking cessation, with no focus on weight (STANDARD).

Within each of those groups, the patients were then randomized to receive either bupropion or a placebo. The bupropion group received sustained release 150 mg tablets administered once daily for the first two days and twice daily for the remainder of the 26-week treatment period. The primary outcomes were the rate and duration of biochemically verified prolonged abstinence. Secondary outcome measures included point prevalent abstinence, post-cessation weight gain, changes in nicotine withdrawal, depressive symptoms and weight concerns.

Overall, 31.8%, 21.8% and 16.3% of the women met the criteria for prolonged abstinence at three, six and 12 months, respectively. Women in the CONCERNS plus bupropion group were significantly more likely than those in the CONCERNS plus placebo group to maintain abstinence at three, six and 12 months ( $p=0.001$ ,  $p<0.001$  and  $p=0.006$ , respectively). In contrast, bupropion therapy did not confer significant benefit during the period of active drug treatment for those receiving STANDARD counseling.

Cessation rates at three and six months were larger for the STANDARD plus bupropion group than for the STANDARD plus placebo

subjects, although these rates were not significant. At 12 months, a difference in abstinence rates favored the STANDARD plus bupropion treatment over the STANDARD plus placebo treatment ( $p=0.05$ ). No significant differences were seen among abstinent women in post-cessation weight gain.

**Conclusion:** This study of women smokers who were concerned about weight gain found that a combination of cognitive behavioral therapy focusing on weight concerns and bupropion provided a better opportunity for smoking cessation than traditional therapy with or without medication.

Levine, M., et al. Bupropion and Cognitive Behavioral Therapy for Weight Concerned Women Smokers. *Arch Int Med.* 2010, March 22; 170 (6): 543-550.

#### UPPER INTENSITY LIMIT FOR AEROBIC EXERCISE IN CHRONIC HEART FAILURE

Reduced exercise capacity is the clinical hallmark of chronic heart failure (CHF). The term "critical power" has been proposed to describe the upper limit of prolonged aerobic performance above the ventilatory anaerobic threshold that is the highest power sustainable in conditions of  $\dot{V}O_2$  and lactate steady-state. This study sought to measure critical power in a group of elderly patients with CHF, in order to define the upper intensity limit for continuous aerobic training.

The study involved 15 patients with CHF and 10 without. All subjects underwent ergonomic evaluation, as well as a ramp incremental cardiopulmonary exercise test. The participants then underwent one incremental, and five, very high intensity, constant power, cardiopulmonary exercise tests. Using these tests, the critical power was calculated. The subjects then underwent one constant power test performed at the individual's critical power. Blood samples were collected every two minutes during exercise at the critical power to assess for lactate levels.

The critical power values were 80 in the patients with CHF, 129 in untrained normal subjects and 199 in trained normal subjects ( $p<0.005$  for all). These values correspond to

66%, 66% and 74% of peak power in the CHF, untrained normal and trained normal groups, respectively.

**Conclusion:** This study suggests that the upper intensity limit for prolonged aerobic exercise in patients with chronic heart failure is 65% of peak power.

Mezzani, A., et al. Upper Intensity Limit for Prolonged Exercise in Chronic Heart Failure. *Med Sci in Sp and Exer.* 2010, April; 42(2): 633-639.

#### EFFECTS OF WEIGHT LOSS WITH VERY LOW CARBOHYDRATE AND LOW FAT DIETS

Although current weight-loss recommendations are to consume a moderate, hypocaloric, high carbohydrate, low-fat diet, the obesity epidemic has led to a rise in the use of alternative dietary patterns, particularly very low carbohydrate diets. Brachial artery flow-mediated dilatation (FMD) is a functional marker of endothelial function, which is impaired in obesity. Previous meal studies have shown that a high saturated fat meal can impair FMD. Conversely, two further studies have shown that a Mediterranean, high monounsaturated fat diet can improve FMD. This study compared the effects of an energy restricted, high saturated fat low carbohydrate diet with an isocaloric low fat diet on FMD and markers of vascular function after 12 months.

One hundred eighteen volunteers, ranging in age from 24 to 64 years, all with a body mass index of between 26 and 43, were randomized to consume either an energy restricted, high saturated fat, low carbohydrate diet (LC) or an isocaloric, conventional, low fat high carbohydrate diet (LF). Those on the LC diet were prescribed a dietary plan that provided four percent of total energy from carbohydrates, 35% from protein and 61% from fat, with the objective to restrict carbohydrate to less than 20 g per day during the first eight weeks, rising to no more than 40 g per day for the remainder of the study. Those on the LF diet consumed 46% of total energy as carbohydrate, 24% as protein and 30% as fat, with the objective to restrict saturated fat to less than 10 g per day for the study's duration. Body weight, endothelial derived factors,

(Continued from page 2)

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FMD, adiponectin, the augmentation index and pulse wave velocity were all assessed.

Energy intake was similar, and by week 52, the magnitude of weight loss also similar, in both diet groups. Following the intervention, there was a significant treatment and time effect ( $p=0.045$ ), such that FMD decreased in the LC diet but remained unchanged in the LF diet group. Subjects in the LC group had greater increases in total cholesterol and LDL-C ( $p<0.05$ ). At one year, participants in the LC diet also had a greater reduction in triglycerides and increase in HDL, although those findings did not reach statistical significance ( $p<0.07$ ).

**Conclusion:** This study found that low fat and low carbohydrate diets have a similar capacity for weight reduction, although these data suggest that chronic consumption of a low carbohydrate diet may have detrimental effects on endothelial function.

Wycherley, T., et al. Long-Term Effects of Weight Loss with Very Low Carbohydrate and Low Fat Diets on Vascular Function in Overweight and Obese Patients. *J Int Med.* 2010, May; 267(5):452-461.

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