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SOMATOSENSORY DEFICITS IN POST-ACL RECONSTRUCTION PATIENTS

The anterior cruciate ligament (ACL) plays a key role in the central somatosensory feedback loop by providing information about knee joint position. As somatosensory deficits in the knee have been found in patients following ACL reconstruction (ACLR), this study was designed to determine whether somatosensory changes are also present in the joints distal to the knee.

This case-controlled study included 30 subjects (15 in the ACLR group and 15 matched controls). Cutaneous detection threshold testing was completed for all participants using a monofilament at four locations, the plantar first metatarsal, the base of the fifth metatarsal, the medial malleolus, and the lateral malleolus. Subjects were prone with noise cancelling headphones and were instructed to say "yes" at any point a monofilament was perceived. Testing demonstrated good reliability; however, examiners were not held blind to group status.

Compared to controls, more diminished cutaneous detection thresholds were found in the ACLR group at both the first metatarsal ($p < 0.001$) and the medial malleolus ($p = 0.002$). There were no differences between groups in demographic variables, except for NASA physical activity scores, which were slightly higher in the ACLR group.

Conclusion: This study suggests that individuals who have undergone anterior cruciate ligament reconstruction experience somatosensory impairments at the foot and ankle.

Hoch J.M., et al. Somatosensory Deficits in Post-ACL Reconstruction Patients: A Case-Control Study. *Muscle Nerve*. 2017, January; 55(1): 5-8.

NECK PAIN AND CERVICAL DYSTONIA TREATED WITH BOTULINUM TOXIN A

For cervical dystonia (CD), botulinum toxin injections in selected muscles is the treatment of choice. This study was designed to identify clinical outcomes related to pain in patients with CD treated with botulinum toxin (BoNT).

Data were obtained from an open label, prospective, multicenter clinical registry of patients with CD treated with BoNT. All subjects had a diagnosis of CD, were new to BoNT treatment or had not received such treatment for at least 16 weeks. Dosing in the muscles injected was at the discretion of the treating physician. Patients were assessed with the Pain Numeric Rating Scale, the Pain subscale of the Toronto Western Spasmodic Torticollis Rating Scale, the Pain subscale of the Toronto Western Spasmodic Torticollis Rating Scale and the Pain and Discomfort subscales of the Cervical Dystonia Impact Profile.

The study enrolled 1,046 subjects, of whom 95% reported neck pain or discomfort prior to the injections. Post-injection pain relief ranged from 67.1% after the first treatment to 76.4% after the third treatment. The average time to pain relief ranged from 7.6 days after the first and 7.1 days after the third treatment. For those reporting moderate to severe neck pain at baseline, all pain scales demonstrated significant reductions in pain levels between baseline and final follow-up ($p < 0.0001$).

Conclusion: This study of patients with pain related to cervical dystonia found that those with moderate to severe neck pain experienced significant pain relief after BoNT injections.

Charles, P., et al. Neck Pain and Cervical Dystonia: Treatment Outcomes from CD PROBE (Cervical Dystonia Patient Registry for

Observation of OnabotulinumtoxinA Efficacy). *Pain Pract.* 2016, November; 16(8): 1073-1082.

TINNITUS AND RADIOFREQUENCY ABLATION

Tinnitus is difficult to diagnose and treat, as it can originate from the auditory, neurologic or vascular systems. This study assessed the efficacy of percutaneous radiofrequency treatment of the superior cervical sympathetic ganglia (SCSG) for patients with tinnitus.

Subjects were 251 consecutive patients with tinnitus undergoing SCSG. Baseline data included age, gender and tinnitus characteristics, comorbidities and self-reported benefit from treatment after seven weeks. Audiograms were used to evaluate hearing. Patients were contacted by telephone by an independent observer to determine long-term outcomes.

Of the 251 patients, 239 had a test blockade first, with 41% of these responding positively. Of these, 83 underwent radiofrequency lesions, with 64% of these noting a reduction in their tinnitus. Of those successfully treated, a continued relief of tinnitus was noted in 50% at 18 months and in 40% at two years. Of the responders, 57% rated their relief as moderate, 32% as good, and 11% as very good. Positive relief with treatment was more often found among females, and among those reporting dizziness at baseline. Hearing loss correlated with a positive effect of treatment.

Conclusion: This study of patients with tinnitus found that radiofrequency ablation of the superior cervical sympathetic ganglion can reduce symptoms in most of the patients who respond positively to a test blockade.

Koning, H., et al. Percutaneous Radiofrequency Lesion of the

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Superior Cervical Sympathetic Ganglion in Patients with Tinnitus. **Pain Practice.** 2016, November; 16 (8): 994-1000.

PCSK9 AND HMGCR AND RISK OF CARDIOVASCULAR DISEASE OR DIABETES

Monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9) have been found to significantly reduce low-density lipoprotein (LDL) cholesterol levels. This literature review was designed to better understand the effect of PCSK9 inhibitors on the risk of cardiovascular events and diabetes.

The study sample included 112,772 participants from 14 prospective cohort or case-control studies. Genetic scores were constructed for PCSK9 and HMGCR (the target of statins) variants that were associated with LDL cholesterol levels at a genome wide level of significance. The LDL cholesterol-lowering alleles of each subject were combined after weighting each by the magnitude of the effect of each variant on LDL cholesterol levels. The subjects were divided by those who were either above or below the median of these weighted scores. These groups were compared for the occurrence of first myocardial infarction or death from coronary heart disease, with the primary safety outcome of diabetes.

Those with higher PCSK9 scores had lower mean LDL cholesterol scores than did those with lower PCSK9 scores, with similar findings for levels of triglycerides, and higher mean levels of HDL cholesterol. Those with higher PCSK9 scores had an 8.4% lower risk of myocardial infarction or death from coronary heart disease (OR 0.92). In a similar analysis, using HMGCR scores, those with higher scores had mean LDL cholesterol levels that were lower than those with lower HMGCR scores. These subjects had a 6.6% lower risk of myocardial infarction or death from coronary heart disease (OR 0.93). In addition, both PCSK9 and HMGCR genetic scores had a dose dependent effect, increasing the risk of diabetes.

Conclusion: This study found that variants of PCSK9 and HMGCR were associated with the risk of cardiovascular events and diabetes, with these effects additive. The

authors suggest that inhibitors of PCSK9 will likely have the same effect as statins on the risk of cardiovascular disease and diabetes.

Ference, B., et al. Variation in PCSK9 and HMGCR and Risk of Cardiovascular Disease and Diabetes. **N Engl J Med.** 2016, December 1; 375(22): 2144-2153.

WORLDWIDE BLOOD PRESSURE TRENDS

Elevated blood pressure is a leading risk factor for cardiovascular diseases as well as chronic kidney disease. In 2013, the World Health Assembly targeted the lowering of the prevalence of elevated blood pressure by 25% by 2025. This study was designed to estimate the global trends in blood pressure between 1975 and 2015.

This pooled analysis included data collected from samples of national, subnational and community studies in which blood pressure had been measured. From these data, estimates were made of trends from 1975 to 2015 in mean systolic (SBP) and mean diastolic blood pressure (DBP).

From 1,479 population-based measurement surveys and studies involving 19.1 million participants, estimates were made for 97.5% of the world's population in 2015. Globally, age standardized adult mean SBP and DPB remained virtually unchanged between 1975 and 2015 in both men and women. The mean blood pressure in high income Western and high income Asia-Pacific super regions improved such that these two regions moved from being among those with the highest blood pressure in 1975 to the lowest in 2015. The highest level blood pressure has shifted in these four decades from high income countries to low income and middle income countries in Southeast Asia and sub-Saharan Africa.

Conclusion: This study demonstrates that, while the average blood pressure in the world has not changed significantly in the past 40 years, regions with relatively higher blood pressures have shifted from high income countries to low income countries in Southeast Asia and sub-Saharan Africa.

NICD Risk Factor Collaboration. Worldwide Trends in Blood Pressure from 1975 to 2015: A Pooled Analysis of 1,479 Population-Based Measurement Studies with 19.1 Million Participants. **Lancet.** 2017, January 7; 389: 37-55.

MEDITERRANEAN DIET AND BRAIN STRUCTURE

Previous studies have demonstrated the potential health benefits of a Mediterranean-type diet (MeDi), with high consumption of fruits, vegetables, legumes and cereals, with olive oil as the primary source of fat, and with a moderate consumption of fish and a low intake of red meat. Increased adherence to the MeDi has been linked to better cognitive function and a reduced risk of Parkinson's disease and Alzheimer's disease. This prospective study examined structural brain imaging data to measure the association between adherence to the MeDi and multiple indices of brain structural aging.

Subjects were participants in the Lothian Birth Cohort, all born in 1936 in the Edinburgh region of Scotland. Using the Scottish Collaborative Group 168-Item Food Frequency Questionnaire, adherence to the MeDi was calculated and scored, with higher scores indicating higher adherence. All subjects underwent MRI evaluation of the brain at the ages of 73 and 76 years, with these results compared with the MeDi adherence scores.

Using regression analysis, with adjustments made for demographic and physical health indicators, adherence to the MeDi was *inversely* associated with a greater three-year reduction in total brain volume. When analyzing fish and red meat consumption separately, no associations were found with this consumption and total brain volume or gray matter volume changes.

Conclusion: This prospective Scottish study found a protective association between adherence to a Mediterranean diet and brain atrophy.

Luciano, M., et al. Mediterranean-Type Diet in Brain Structural Change from 73 to 76 Years in a Scottish Cohort. **Neurol.** 2017, January 31; 88: 2-7.

METABOLIC SYNDROME AND POLYNEUROPATHY

Polyneuropathy is thought to affect two to seven percent of the population. The most common etiology is diabetes. This study was designed to better understand the prevalence of polyneuropathy as it relates to glycemic status in obese and lean populations.

Between November of 2010 and December of 2014, adult patients with a body mass index of 35 kg/m² or greater, each seen at the University of Michigan Weight Management Program, were invited to participate in this study. At baseline all subjects underwent a workup, including a history and physical examination, with testing including glucose tolerance tests, lipid panels and morphometric evaluation. Diabetic status and metabolic profiles were also recorded. Polyneuropathy was identified by the Toronto consensus definition of probable polyneuropathy. To clarify peripheral nerve function, various nerve conduction studies were completed. The primary analysis involved the presence of polyneuropathy compared with components of the metabolic syndrome.

Data were obtained from 102 obese patients and 79 lean controls. The prevalence of polyneuropathy among those with normoglycemia was 3.8% in the lean control group and 11.1% in the obese group, 29% in obese participants with prediabetes and 34.6% in obese patients with diabetes (p<0.01). In the multi-variable logistic regression analysis, age and waist circumference were significantly associated with polyneuropathy.

Conclusion: This study found a high prevalence of polyneuropathy among obese patients, even among those with normoglycemia.

Callahan, B., et al. Association between Metabolic Syndrome Components and Polyneuropathy in an Obese Population. **JAMA Neurol.** 2016, December; 73(12): 1468-1476.

PLANTAR FASCIITIS TREATED WITH BOTULINUM TOXIN

Plantar fasciitis affects up to ten percent of individuals at some point in life. When conservative measures are ineffective, other nonoperative

treatments have included extracorporeal shockwave therapy and platelet rich plasma injections. However, even among those who undergo surgical intervention, 50% continue to experience significant dysfunction and/or pain. Previous studies have suggested that botulinum toxin may be effective for treating plantar fasciitis, although those studies have been limited by short follow-up. This study assessed the effect of botulinum toxin for long-term pain relief.

Subjects were 50 patients with recalcitrant plantar fasciitis, randomized to receive either Incobotulinumtoxin A (IBTA) or saline injections to the affected foot. Before and after intervention, the patients were assessed with the Foot and Ankle Ability Measures (FAAMs) and a visual analog scale (VAS). The patients were followed after the injections at six and 12 weeks and then at six and 12 months.

At six months post-injection, the mean FAAM score increased in the IBTA group from 36.3/100 to 73.8/100. The mean VAS pain score decreased in the IBTA group from 7.2/10 to 3.6/10. Both of these differences in functional and pain scores are significantly better than before injection, as well as when compared with the placebo group at six and 12 months post-injection (p=0.01 for all comparisons). At 12 months, 12% of the placebo group and zero percent of the IBTA group opted for surgical intervention.

Conclusion: This prospective, randomized, double-blind study found that IBTA can provide significant relief from pain and dysfunction due to plantar fasciitis, with this relief persisting at one year.

Ahmad, J., et al. Treatment of Plantar Fasciitis with Botulinum Toxin: A Randomized, Controlled Study. **Foot Ankle Int.** 2017, January; 38(1): 1-7.

BOTOX IN THE MASSETER FOR TENSION HEADACHES

Tension-type headaches are among the most common spontaneous, primary headaches. These are often accompanied by temporomandibular joint (TMJ) dysfunction and masseter pain. This study was designed to assess the efficacy of botulinum toxin type A (BTXA) injections in patients with

masseter muscle pain, TMJ dysfunction and tension-type headache.

This prospective study included 42 adults with TMJ dysfunction and tension-type headaches. The patients received 21 units of Botox in the masseters, at the area of the greatest cross-section surface. The subjects were assessed for pain at one week before treatment and 24 weeks after treatment with a VAS (Visual Analogue Scale) and a VNRS (Verbal Numerical Rating Scale).

At 24 weeks, headache intensity, as measured by both pain scales, had significantly decreased ($p=0.0000$). After treatment, the patients reported a decrease in the use of analgesic drugs, as well as a decrease in pain duration with headaches ($p=0.0000$ for all comparisons).

Conclusion: This study of patients with temporomandibular joint dysfunction and tension-type headaches found that botulinum toxin injections into the masseter muscle could decrease the frequency and intensity of headaches.

Pihut, M., et al. The Efficiency of Botulinum Toxin Type A for the Treatment of Masseter Muscle Pain in Patients with Temporomandibular Joint Dysfunction and Tension-Type Headache. *J Headache Pain*. 2016; 17: 29.

MODIFIED FLIP-FLOPS AND FOOT PAIN

Recent studies have estimated that one in five people over 45 years of age experience frequent foot pain. This study reviewed the efficacy of flip-flop style footwear, with a molded foot bed, for reducing pain and improving function among adults with disabling foot pain.

Adult subjects were recruited who reported disabling foot pain, defined as pain with restriction of at least one normal activity. Exclusion criteria included peripheral artery disease, venous insufficiency or peripheral neuropathy. Those randomized to an intervention group were fitted with flip-flops with a molded foot bed, heel cup and wide straps. They were asked to wear this footwear as much as possible for the next 12 weeks. Those in a control group were asked to wear their usual footwear. The primary outcome measure was the

foot pain domain of the Foot Health Status Questionnaire (FHSQ). Secondary outcome measures included current foot pain (VAS) as well as the FHSQ domains of foot function and general foot health.

Of the subjects recruited, 54 were allocated to the treatment and 54 to the control group. Compared to the control group, the treatment group had significant improvement in pain at 12 weeks, as measured by the foot pain domain of the FHSQ ($p<0.01$). In addition, the treatment group obtained significantly better scores on the pain VAS ($p<0.01$), the FHSQ domain of function ($p<0.01$) and the FHSQ domain of general foot health ($p<0.01$).

Conclusion: This study of patients with disabling foot pain found that the use of flip-flops, with a contoured bed, resulted in significant improvement in pain and function.

Chuter, V., et al. Flip-Flop Footwear with a Molded Foot Bed for the Treatment of Foot Pain: A Randomized, Controlled Trial. *BMC Musculoskelet Disord*. 2016, Nov 11; 17: 468.

COMPUTERIZED COGNITIVE EXERCISE FOR MODERATE TO SEVERE BRAIN INJURY

The benefits of physical exercise are well documented, including improved endurance, strength and overall health. The effects of cognitive exercise in healthy adults or individuals with various medical diagnoses, including cognitive impairment, are less clear. This study explored the feasibility and effects of participation in a computerized cognitive fitness exercise program for a group of adults with chronic, moderate to severe cognitive impairments following acquired brain injury.

A convenience sample of adults with chronic, moderate to severe cognitive impairments from acquired brain injury was used to form two groups. All subjects were assessed with a neurocognitive test battery, administered twice before beginning a five-month exercise program and within a week of the program's end. Those in the exercise program used brainHQ, a commercially available, online, computerized cognitive exercise program consisting of six categories of cognitive function. After

an orientation session, the participants were asked to participate five days a week, 60 minutes per session, for five months.

Of the initial participants, five in the experimental group and seven in the control group completed the study. Compared with the control group, the treatment group demonstrated greater improvement on the Hopkins Verbal Learning Test-Revised (HVLT-R) Immediate Recall total words ($p=0.0068$), and on the Word Fluency Task ($p=0.03$). Three of the five in the experimental group reported that performing the computer exercises had improved their everyday thinking abilities, including their memory.

Conclusion: This pilot study of patients with acquired brain injury with moderate to severe cognitive impairment found that a five-month, five days a week, computerized program can improve memory, verbal fluency and life satisfaction.

O'Neil-Pirozzi, T., et al. Feasibility and Benefits of Computerized Cognitive Exercise to Adults with Chronic, Moderate to Severe Cognitive Impairments following an Acquired Brain Injury: A Pilot Study. *Brain Inj*. 2016; 30(13 – 14): 1617-1625.

COGNITIVE STIMULATING ACTIVITIES IN PATIENTS WITH DELIRIUM AND DEMENTIA

Many people with dementia who are hospitalized have persisting delirium superimposed upon their dementia (DSD) at the time of transfer to a post-acute care (PAC) facility. This study was designed to determine whether individualized, cognitive stimulating activities can reduce the duration and severity of delirium and improve outcomes in patients with DSD in a PAC.

Participants with mild to moderate dementia and delirium were recruited after admission to one of eight PAC settings in Pennsylvania. Baseline assessments included physical examination, medication review to determine the Anticholinergic Cognitive Burden Scale and apolipoprotein genotyping. In the treatment group, 15 cognitively stimulating activities were chosen for each individual based upon their leisure interests, physical function and mental status. Intervention

occurred 30 minutes each day, five days a week, for 30 days or until discharge. Delirium duration was measured using the Confusion Assessment Method (CAM), with delirium severity measured using the Delirium Rating Scale. Cognitive and physical functioning were also assessed.

Subjects included 283 patients. The time to achieve two consecutive days without delirium averaged 6.88 days in the treatment group and 7.39 days in the usual care group ($p=0.89$). The treatment group improved more in executive function ($p=0.03$). The average length of stay was 36.1 days for the intervention group and 53.1 days for the usual care group ($p=0.01$). A greater number of intervention participants were discharged to the community (32.6% versus 27.5%).

Conclusion: This study found that, among patients admitted to a post-acute care facility, those with dementia and delirium treated with cognitive stimulating activities did not have a significantly faster improvement in delirium, but did improve in executive function and had a reduced length of stay.

Kolanowski, A., et al. Effect of Cognitively Stimulating Activities on Symptom Management of Delirium Superimposed on Dementia: A Randomized, Controlled Trial. *J Amer Geriatrics Soc.* 2016, Dec; 64 (12): 2424-2432.

LATITUDE AND AGE OF ONSET IN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) has been found to have a higher prevalence as latitude increases. Some have suggested that lower ultraviolet radiation levels and vitamin D deficiency may predispose those genetically at risk. This study examined whether there is a latitude variation of the place of residence at the age of onset of MS, and whether ultraviolet ray levels play a role.

Data were collected from the MSBase registry, a worldwide data set for patients diagnosed with MS. From this registry, 30,415 patients with clinically diagnosed MS were identified, of whom 22,162 were of European descent. The age at onset was compared to the latitude at which the patient lived at the time.

Patients living in a higher latitude were found to be diagnosed with MS at a younger age. For every 10° of latitude increase, the age of onset was found to be 10 months earlier ($p=0.000$). Those in the lowest latitude had an onset at almost two years later than those in the highest latitude. In addition, the data revealed a significant association between lower winter ultraviolet radiation levels and earlier onset of MS ($p<0.001$).

Conclusion: This study of patients of European descent with a diagnosis of MS found that those living at higher latitudes have an earlier age of onset than do those living at lower latitudes.

Tao, C., et al. Higher Latitude Is Significantly Associated with an Earlier Age of Disease Onset in Multiple Sclerosis. *J Neurol Neurosurg Psychiatry.* 2016, November; 87: 1343-1349.

MUSCULOSKELETAL PAIN, BONE MINERAL DENSITY AND PARKINSON'S DISEASE

Pain is a common and distressing problem in Parkinson's disease (PD) that is frequently overlooked. Patients with PD are also known to have reduced bone mineral density (BMD). This study was designed to determine whether an association exists between pain subtypes and BMD in patients with PD.

Patients with PD were recruited from a movement disorder clinic. All underwent clinical evaluation, including pain assessment with a brief pain inventory (BPI), and a visual analog scale (VAS) for pain. A physical examination included determination of body mass index (BMI) and assessment of depression using the Beck Depression Inventory (BDI). Bone mineral density was measured using dual energy x-ray absorptiometry.

Of the 162 patients with PD, 26% reported no pain and 74% reported chronic pain. The most prevalent pain type was musculoskeletal, followed by radicular/neuropathic, dystonic, and central. The BMD studies found osteoporosis and osteopenia in 23.4% and 38.3% respectively in the lumbar spine, 7.4% and 41.3% respectively in the total hip, and 11.7% and 49.3% respectively in the femoral neck. The BMD of the

lumbar spine, total hip and femoral neck were lower among those with musculoskeletal pain than in those without pain ($p<0.001$ for all comparisons). The only association between BMD and central pain was with the BMD scores for the total hip ($p<0.05$).

Conclusion: This cross-sectional study of patients with PD found a significant association between musculoskeletal pain and low bone mineral density.

Choi, S., et al. The Association of Musculoskeletal Pain with Bone Mineral Density in Patients with Parkinson's Disease. *Euro Neurol.* 2017; 77(3-4): 123-129.

PERIPHERAL NERVE BLOCKS FOR HEADACHES

Some have estimated the prevalence primary headache disorders in older adults to be approximately 40.5%. Migraine, while more common in younger individuals, is thought to have a prevalence of two to six percent in the elderly population. This retrospective study assessed the effect of peripheral nerve blocks on headaches in the elderly population.

This retrospective chart review included elderly patients treated with peripheral nerve blocks at the Montefiore Headache Center between 2010 and 2016. A chart review provided data including demographics, headache features and headache frequency. Data gathered from the initial evaluation included headache diagnosis, duration of diagnosis, comorbid medical features and previous treatment.

Sixty-four patients met the inclusion criteria, with an average age of 71 years. The average number of headache days per month at the time of the first injection was 23. The patients received an average of four peripheral nerve blocks, with 70% receiving blocks to the bilateral greater and lesser occipital nerves and bilateral auriculotemporal, supraorbital and supra-trochlear nerves. The blocks were determined to be effective in 73% of the patients, including 81% with chronic migraine, 73% with episodic migraine, 67% with chronic tension type headache, 60% with occipital neuralgia and 50% with trigeminal autonomic cephalalgia.

Conclusion: This retrospective study of patients 65 years of age and older found that peripheral nerve blocks can be effective for a range of headache diagnoses.

Hascalovici, J., et al. Peripheral Nerve Blocks for the Treatment of Headache in Older Adults: A Retrospective Study. **Headache**. 2017, January; 57: 80-86.

CIRCADIAN RHYTHM OF MELATONIN AFTER TBI

Patients with traumatic brain injury (TBI) often complain of sleep difficulties, including sleep initiation, maintenance and overall sleep quality. As research has demonstrated that melatonin production may be altered after a TBI, this study compared the melatonin circadian rhythm in patients with TBI with that of normal controls.

Subjects were patients with TBI who were diagnosed with chronic insomnia. The control group had no history of TBI or poor sleep quality. After determining the subjects' normal sleep patterns, saliva samples were collected hourly for melatonin analysis, beginning seven hours prior to the participant's habitual bedtime. The primary outcome variable was total, overnight melatonin production. Secondary outcomes included circadian phase, measured by dim light melatonin onset (DLMO), melatonin synthesis onset (SynOn) and offset (SynOff).

Data were obtained for 10 patients with TBI and 10 controls. Overnight melatonin production was 42% lower in patients with TBI than in controls. The timing of melatonin synthesis, as measured by both DLMO and SynOn, was significantly later in patients with TBI. No significant differences were noted between the groups in Epworth Sleepiness Scale scores, while the TBI group obtained higher Pittsburgh Sleep Quality Index scores.

Conclusion: This study of patients with TBI found that, compared with controls, melatonin production was reduced overnight, with the timing of the melatonin production delayed among those with TBI.

Grima, N., et al. Circadian Melatonin Rhythm Following Traumatic Brain Injury. **Neurorehab Neural Repair**.

2016, November /December; 30(10): 972-977.

CHONDROITIN SULFATE AND GLUCOSAMINE SULFATE FOR KNEE OSTEOARTHRITIS

Results from the glucosamine/chondroitin arthritis intervention trial (GAIT) failed to demonstrate that this intervention could reduce joint pain among patients with osteoarthritis (OA) of the knee. A subsequent analysis, however, suggested that this intervention might be effective in a subset of patients with moderate to severe knee pain. This study was designed to better assess this treatment as compared with placebo for painful knee OA.

This phase three, multicenter, randomized, double-blind, placebo controlled, parallel group trial included patients with primary symptomatic knee OA. Participants had radiographic grade 2 or grade 3 knee OA according to the Kellgren/Lawrence scale. The 164 participants were randomly assigned to receive a placebo or oral glucosamine/chondroitin sulfate (CS/GS) 1,200 /1,500 mg daily for six months. All subjects were assessed for pain using a visual analog scale, with secondary outcomes including investigators' global assessments of disease activity and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores.

A modified intent to treat analysis revealed that the treatment group had significantly less reduction in pain scores than did the placebo group ($p=0.029$). Both groups improved on total WOMAC scores, as well as on the Pain and Function subscales of the WOMAC, with no significant difference between the groups.

Conclusion: This study of patients with osteoarthritis of the knee did not find that the oral combination of chondroitin sulfate and glucosamine sulfate is effective for reducing pain and improving function over six months.

Roman-Blas, J., et al. Combined Treatment with Chondroitin Sulfate and Glucosamine Sulfate Shows No Superiority over Placebo for Reduction of Joint Pain and Functional Impairment in Patients with Knee Osteoarthritis: A Six-Month Multicenter, Randomized,

Double-Blind, Placebo Controlled Trial. **Arthritis Rheumatol**. 2017, January; 69(1): 77-85.

EXERCISE, SEVERE FATIGUE AND CANCER TREATMENT

While a number of studies have suggested that physical exercise can alleviate fatigue among patients with cancer, few randomized trials have been conducted. This study compared standard of care treatment to self-directed and partially supervised exercise programs among patients with cancer.

Patients were recruited from the oncology ward of a University Hospital between 2012 and 2014. Eligible subjects were cancer patients, either undergoing active treatment or within three months of completing chemotherapy. The participants were randomized to one of three treatment groups. Group A received treatment as usual, with no additional exercise. Groups B and C were taught exercise by a physical therapist in a structured individual program over 12 weeks. The exercise program was five, 20- to 30-minute sessions per week, with three times endurance and two times strength training. Group C was asked to receive additional physical therapy treatment near home twice per week. At 12 weeks from the onset of intervention, the patients were invited for a second assessment and asked to submit activity diaries. All subjects were assessed with the Multidimensional Fatigue Inventory (MFI), the Six-Minute Walkway Test and the International Physical Activity Questionnaire-Short Form.

At 12 weeks' follow-up, mean scores on the MFI were nonsignificantly different between the groups. As compared to group A, a significantly greater reduction of mental fatigue was found in group B. A trend of declining mental fatigue, as well as a trend of increased activity, was also found in group C.

Conclusion: This study of patients with cancer found that exercise, five days per week can reduce mental fatigue and increased activity in this population.

Schuler, M., et al. Impact of Different Exercise Programs on Severe Fatigue in Patients Undergoing Anticancer Treatment: Randomized Controlled Trial. **J Pain Symptom**

Manage. 2017, January; 53(1): 57-66.

GOLF AND HEALTH

It is estimated that golf is played by 55 million people worldwide. A recent review of the health benefits related to sport suggests that the evidence is conclusive only for soccer and running, with no clear evidence for the health benefits of golf. This study reviewed both published and unpublished studies to estimate the health benefits of participation in golf.

The literature was reviewed for primary research studies, reviews, systematic reviews, scoping reviews, meta-analyses, guidelines and "gray" literature, including unpublished and ongoing trials, reports, dissertations and conference proceedings. From the search, 301 studies including golf and health were chosen for analysis.

Of the 301 studies identified, 59% were primary research, 30% were secondary studies and 11% were gray literature. Those studies that estimated metabolic equivalents of task (MET) found that the METs ranged from 2.5 to 8.0. Calorie expenditure when walking ranged from 531 to 2,467 kcal per 18 holes. No studies directly measured the effects of golfing on health, although one study suggested a reduced mortality.

Conclusion: This review of the literature found that golf provides moderate intensity aerobic physical activity, and may have health benefits including reduced mortality.

Murray, A. The Relationship between Golf and Health: A Scoping Review. *Br J Sports Med.* 2017; 51; 1:12-19.

NEUROCHEMISTRY OF REPETITIVE MILD TRAUMATIC BRAIN INJURY

While the symptoms of concussion usually resolve within days to weeks, 10-15% will experience neurological symptoms persisting beyond three months. Some with repetitive mTBI may develop chronic traumatic encephalopathy (CTE). As CTE shares similar histopathological changes with other neurodegenerative diseases this study was designed to better

understand the pathophysiology of the post-concussive syndrome (PCS).

This multicenter cross-sectional study involved 16 male professional ice hockey players with PCS for more than three months and 15 neurologically healthy controls. All subjects underwent neuropsychological assessment and cerebral spinal fluid collection as well as physical and neurologic exam. The CSF was assessed for neurofilament light protein (NF-L) and glial fibrillary acid protein concentrations of A β 1-42, T-Tau, and P-Tau.

Compared with the control group, concentrations of NF-L were increased in the PCS group, although this finding did not reach statistical significance. Significant relationships were seen between lifetime concussion events and NF-L, as well as P-Tau. Levels of A β 1-42 were significantly lower in the PCS group than in the control group (p=0.05). Those with PCS for more than one year had lower concentrations than those whose symptoms resolved within one year (p=0.01).

Conclusion: This small study of professional ice hockey players found that those with post-concussion syndrome had increased levels of CSF NF-L and reduced levels of A β 1-42 suggestive of axonal white matter injury and amyloid deposition.

Shahim, P., et al. Neurochemical Aftermath of Repetitive Mild Traumatic Brain Injury. *JAMA Neurol.* 2016, Nov 1; 73(11): 1308-1315.

LONG-TERM OPIOID USE AND REPRODUCTIVE DYSFUNCTION

Chronic noncancer pain (CNCP) is defined as any painful condition lasting for three months or longer that is not associated with neoplastic disease. Among patients with CNCP, 12-13% are prescribed opioids. As chronic opioid use in men has been found to be associated with hypogonadism and reproductive dysfunction, this literature review was designed to better clarify CNCP-related dysfunction among women with long-term prescription opioid use.

Databases were reviewed for studies including women 18 to 55 years of age, involving opioids and genetic and reproductive side effects. From this review, six studies involving

oral, five studies involving intrathecal and one study involving transdermal opioids were identified for inclusion.

Of the 10 studies reviewing menstrual cycle changes, 23% to 81% of women taking oral or intrathecal opioids had menstrual cycle abnormalities. This was not true in a study of women using transdermal buprenorphine. Of the three articles reviewing libido, reduced libido was found in 61% to 100% of patients taking opioids, although a reduction was also noted among controls. Only two of the ten studies reviewing hormone levels found a significant decrease in levels.

Conclusion: This literature review of premenopausal adult women taking oral or intrathecal long-term opioids found that these women were more likely to have clinical symptoms of hypogonadism with reduced levels of hormones.

Wersocki, E., et al. Comprehensive Systematic Review of Long-Term Opioids in Women with Chronic Noncancer Pain and Associated Reproductive Dysfunction (Hypothalamic-Pituitary-Gonadal Axis Disruption). *Pain.* 2017, January; 158 (1): 8-16.

IMMEDIATE AND DELAYED LOWER LIMB AMPUTATION COMPARED TO SALVAGE

Functional outcomes of amputees are often comparable with those in the age matched general population. This study compared the outcomes of patients who underwent immediate unilateral amputation to those of patients who underwent delayed unilateral amputation and those who underwent lower limb salvage.

This retrospective analysis involved a cohort of military patients undergoing posttraumatic lower limb salvage or amputation between January 2013 and January 2015. The majority were soldiers involved in the wars in Iraq or Afghanistan. Injury severity was determined at the time of injury, with demographics, length of hospitalization, and comorbidities also recorded. Patients were assessed for functional outcome and mental health outcome measures.

Of the 100 military personnel included in the study, 11 underwent immediate below knee amputation, 15 delayed below knee amputation, 10 immediate above knee

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amputation, 43 bilateral amputation and 21 limb salvage. The mean time between injury and amputation in the delayed group was 10 months. The immediate above knee and below knee amputation group required a significantly greater number of months of rehabilitation than did the delayed below knee amputation and the limb salvage group ($p < 0.05$). At completion of rehabilitation, those with unilateral amputation could walk significantly farther in the 6 minute walk test than those with limb salvage and those with bilateral amputation ($p < 0.05$).

Conclusion: This study of British military veterans found that those electing for delayed amputation after limb salvage attempts achieved superior functional gains than did those who underwent limb salvage only, with equivalent outcomes to those with immediate amputation.

Ladlow, P., et al. Influence of Immediate and Delayed Lower Limb Amputation Compared with Lower Limb Salvage on Functional and Mental Health Outcomes Post-Rehabilitation in the UK Military. *J Bone Joint Sur.* 2016, Dec 7; 98 (23): 1996-2005.

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