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INFECTIOUS BURDEN AND ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is thought to be the most common type of age related dementia. The pathogenesis of familial AD has not been well established beyond beta-amyloid plaque deposition. As previous studies have suggested that the overall burden of prior infections contributes to cardiovascular diseases, as well as stroke, this study was designed to determine the association between infectious disease burden and AD.

Participants were 128, consecutive patients with AD and 135 age- and gender-matched controls with normal cognition. All participants were tested with the Mini-Mental State Examination (MMSE). Infectious burden (IB) was measured using antibody titers of the infectious agents, B. Burgdorferi, C. pneumoniae, H. pylori, CMV and HSV -1. Serum interleukin-1β (IL-1β), IL-6, tumor necrosis factor and serum beta amyloid protein (Aβ40 and Aβ42) levels were also measured. Infectious burden was defined as a composite serological measure of exposure to these common pathogens.

A logistic regression analysis showed that increased total IB is independently associated with AD (odds ratio 1.86). Higher IB was specifically associated with higher beta-amyloid levels and lower MMSE ($p< 0.001$) among both patients with AD and controls.

Conclusion: This prospective study suggests that the cumulative infectious burden is a significant indicator of overall inflammation, and likely plays a role in pathogenesis of Alzheimer's disease.

Bu, X., et al. A Study on the Association between Infectious Burden and Alzheimer's Disease. **Euro J Neurol.** 2015, December; 22 (12): 1519-1525.

ANDEXANET ALFA FOR REVERSAL OF FACTOR XA INHIBITOR

Direct factor Xa inhibitors are relatively new agents for the prevention of stroke in patients with nonvalvular atrial fibrillation (a-fib), and for the treatment and secondary prevention of venous thromboembolism. Despite the efficacy of these inhibitors, the lack of a specific antidote to reverse their anticoagulant effects has been an important limitation to their use. This study reviewed the effect of andexanet, a recombinant modified human factor Xa decoy protein that binds factor Xa inhibitors in the active site with high affinity.

Healthy, older volunteers were randomized to receive either five mg of apixaban orally twice daily or 20 mg of rivaroxaban daily for up to four days to achieve steady-state plasma levels. Three hours after the last dose on day four, andexanet was administered as an IV bolus, followed by continuous infusion for 120 minutes. The primary endpoint was the percent change in anti-factor Xa activity.

Anti-factor Xa activity was rapidly reduced, within two to five minutes after the administration of andexanet, in both the apixaban study and the rivaroxaban study. Thrombin generation was restored to within the normal range within 2-10 minutes in 100% of the apixaban and 96% of the rivaroxaban groups ($p<0.001$ for both comparisons). No serious adverse events and no thrombotic events were reported.

Conclusion: This study of patients receiving factor Xa inhibitors found that andexanet could reverse anticoagulant activity within minutes of administration.

Siegal, D., et al. Andexanet Alfa for the Reversal of Factor Xa Inhibitor Activity**. New Engl J Med.** 2015, December; 17(25): 2413-2424.

INTENSIVE VERSUS STANDARD BLOOD PRESSURE CONTROL

The Global Burden of Disease Study identified elevated blood pressure as the leading risk factor for death and disability adjusted life years lost during 2010. This study describes the results of the Systolic Blood Pressure Intervention Trial (SPRINT), which compared the benefit of treating SBP to a target of less than 120 mmHg with treatment to a target of less than 140 mmHg.

This randomized, controlled, open label trial included patients at least 50 years of age with a SBP of 130 to 180 mm Hg and an increased risk of cardiovascular events. Participants were randomly assigned to a group targeting SBP of less than 140mmHg (standard treatment group) or less than 120 mmHg (intensive treatment group). The treatment algorithm was provided to the providers, with all major classes of antihypertensive agents provided at no cost to the participant. The primary outcome measure was a composite of myocardial infarction, acute coronary syndromes, stroke, heart failure or death from cardiovascular causes. Secondary outcomes included the individual components of the primary composite outcome, death from any cause and the composite of the primary outcome or death from any cause.

At one year, the primary outcome measure was confirmed in 243 in the intensive treatment group and 319 in the standard treatment group ($p<0.001$). Of the recorded deaths, 155 occurred in the intensive treatment group and 210 in the standard treatment group ($p=0.003$). The relative risk of death from cardiovascular causes was 43% lower in the intensive intervention group ($p=0.005$). There was no significant difference between groups in serious adverse events.

Conclusion: This study of patients at high risk for cardiovascular

events, without diabetes, found that targeting systolic blood pressure of less than 120 mmHg results in lower rates of fatal and nonfatal cardiovascular events and death from any cause, as compared with blood pressure targeted at 140 mmHg.

The Sprint Research Group. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. **New Engl J Med**. 2015, November 26; 373(22): 2103-2116.

STROKE OR RECURRENT HEMORRHAGE ASSOCIATED WITH ANTITHROMBOTIC TREATMENT

Patients with non-valvular atrial fibrillation (a-fib) and risk factors for thromboembolism require anti-coagulation to reduce the risk of stroke. Those who experience a gastrointestinal bleeding (GIB) during this treatment face a clinical dilemma regarding whether to restart that treatment. This study assessed the risk of all-cause mortality and hospitalization or thromboembolism associated with the restarting of antithrombotic treatment after GIB in patients with a -fib.

This Danish cohort study included 3,409 patients listed in a national registry from 1996 to 2012. All had suffered a GIB while receiving anticoagulation. The subjects were followed from the date of discharge after a first time admission resulting from the GIB. Patients who died or experienced thromboembolic events or GIB in the first 90 days after discharge were excluded. The participants were then followed for two years for the cumulative incidence of all-cause mortality, thromboembolism, major bleeding and recurrent GIB.

At two years, the cumulative incidences were 39.9% for all-cause mortality, 12% for thromboembolism, 17.7% for major bleeding and 12.1% for recurrent GIB. Of the initial group, 27.1% did not resume antithrombotic treatment after the GIB. Among patients surviving the first 90 days, a reduced risk of all-cause mortality was found among those restarting oral anticoagulation (odds ratio 0.41), an antiplatelet agent (odds ratio 0.76) or oral anticoagulation plus an antiplatelet agent (odds ratio 0.54) compared with the non-resumption group. None of the restarted antithrombotic treatments were associated with a significant increase in the risk of recurrent GIB.

Conclusion: This study of patients with a-fib, hospitalized with a gastrointestinal (GI) bleed, found a two-year mortality rate of 39.9 %. Among those who survived the first 90 days after hospitalization for a GI bleed, restarting oral anticoagulation was associated with the lowest risk of overall mortality and thromboembolism.

Staerk, L., et al. Stroke and Recurrent Hemorrhage Associated with Antithrombotic Treatment after Gastrointestinal Bleed in Patients with Atrial Fibrillation: A Nationwide Cohort Study. **BMJ** 2015; 351: H5876.

RISK OF STROKE WITH ASYMPTOMATIC CAROTID OCCLUSION

In the United States, 90% of carotid interventions are performed on patients with asymptomatic carotid stenosis. In Denmark, the rate is 0%.This study evaluated the risk of stroke among those who progressed to occlusion among patients identified with asymptomatic carotid stenosis.

This retrospective study analyzed data obtained from two Canadian stroke prevention clinics. Patients were seen for annual carotid ultrasounds from 1993 to 1995 and 1995 to 2012, with a final follow-up in 2014. The records of those with occlusion underwent review for prior ultrasound studies and symptoms. As more intensive medical therapy was implemented in 2002 to 2003, that group was evaluated to determine whether aggressive medical therapy, patient characteristics, severity of stenosis and size of plaque impacted the progression to occlusion.

Of the 3,681 clinic patients evaluated, 316 were asymptomatic before the index occlusion occurred. Most of the index occlusions occurred before the initiation of more intense medical therapy. Only one patient had an ipsilateral stroke at the time of occlusion, and only three patients had an ipsilateral stroke during follow-up. Neither the severity of stenosis before occlusion, nor the presence of a prior contralateral carotid occlusion, predicted the risk of stroke events during follow-up after the occlusion.

Conclusion: This study of patients with asymptomatic carotid occlusion found that the risk of stroke after intensive medical therapy is low, well below that found historically with carotid stenting or carotid endarterectomy.

Yang, C., et al. Risk of Stroke at the Time of Carotid Occlusion. **JAMA Neurol.** 2015, November; 72(11): 1261-1267.

MEDICATION OVERUSE HEADACHE AND PRIMARY CARE

Chronic headache affects two to five percent of the population worldwide, with approximately 50% of those with chronic headache having medication-overuse headaches (MOHs). This paper presents data for headache disability, anxiety and depression of MOH patients versus controls, from a study of a brief intervention (BI) for MOH in primary care (the BIMOH study).

This double-blind, pragmatic, cluster, randomized, controlled trial included patients seen by 50 general practitioners in Norway. Subjects were 18 to 50 years of age, with self-reported, chronic headache, all fulfilling the international classification of headache disorders for MOH. Those in the treatment group received a BI, including information on severity of dependence scales and personal risk for MOH, the need to cut down on medication use, the expected gains and the difficulties to be overcome. The general practitioners, in collaboration with their patients, could determine the point where rescue medications and short term sick leave were necessary. The primary outcome variables were numbers of headaches and medication days/month.

Subjects included 60 patients with MOH and 40 controls. Among those with MOH, patients were divided into a BI group or a business as usual (BAU) group Those in the BI group experienced significantly fewer headaches and medication days per month at three months than those in the control group. At follow-up, 67% in the BI group were without medication overuse, with chronic headache resolved in 50%, as compared with three percent and six percent, respectively, in the BAU group.

Conclusion: This study of patients with medication-overuse headaches revealed that those individuals had high levels of disability, with anxiety and depression. Treatment by detoxification by a primary care provider was effective in reducing the number of headaches and degree of medication overuse.

Kristoffersen, E., et al. Disability, Anxiety and Depression in Patients with Medication-Overuse Headache in Primary Care-The BIMOH Study. **Eur J Neurol.** 2016, January; 23 Suppl 1: 28-35.

POSITIVE PRESSURE WALKING FOR KNEE OSTEOARTHRITIS

Osteoarthritis (OA) is a major cause of disability. While exercise is considered important for improving function among patients with OA, data are lacking regarding which types of exercises are best. As lower body positive pressure (LBPP) reduces weight-bearing loads, distributes pressure evenly and allows normal muscle activation patterns, this study was designed to determine whether exercises with body weight support might be better tolerated and more effective than conventional exercise among patients with symptomatic OA.

This prospective study enrolled patients with symptomatic OA and with a body mass index of 25 kg/m² or greater. All had radiographic evidence of mild to moderate OA. Treadmill exercise was performed for 25 minutes at 3.1 m/h, twice weekly. Body weight support was gradually increased until pain reduction was maximized or 40% support was provided. Assessments were made at baseline and at week 12, including Knee Injury and Osteoarthritis Outcome Scores (KOOS), visual analogue scale (VAS) scores of pain and percentage of LBPP support.

Subjects were 31 patients, ages 50 to 75 years. Compared to baseline, overall pain scores improved from 3.2 to 1.8, with eight participants walking pain-free during follow-up walking sessions ($p=0.0001$). In addition KOOS scores improved significantly in subscales of pain , symptoms, ADLs, Sport/Rec and quality of life ($p=0.02$, $p=0.001$, $p=0.007$, $p=0.003$ and $p=0.0002$, respectively).

Conclusion: This study of patients with osteoarthritis of the knee found that lower body positive pressure exercise may result in both functional and pain symptom improvement when treating patients who are overweight or obese.

Peeler, J., et al. Effects of Bodyweight Supported Physical Activity and Joint Pain, Function and Muscle Strength. **Clin J Sports Med**. 2015, November; 25: 518-523.

ADOLESCENT PHYSICAL ACTIVITY AND BONE HEALTH

Research indicates that the optimization of bone accrual in the first few decades of life can reduce the later risk of osteoporosis. This study explored the relationships between physical activity and bone mineral density (BMD) and bone mineral content (BMC) levels.

In the Fit Futures study, all first-year, upper-secondary school students in a defined municipality were invited to participate. Included were 508 girls and 530 boys who underwent height and weight measurements and provided information regarding lifestyle factors. Physical activity frequencies were determined, ranging from never to almost every day. Perceived intensity of activity was categorized into five groups from "a bit hard" to “extremely hard”. Bone parameters, including BMC and BMD, were measured at the total hip, the femoral neck, and for the total body by dual x-ray absorptiometry.

The mean BMD in girls who reported themselves as active outside of school hours was significantly higher at all sites as compared to their inactive counterparts ($p<0.001$). Active girls also had a higher BMC of the femoral neck and total hip ($p<0.001$) as compared to their inactive counterparts. In boys, those reporting to be active had higher BMC and BMD levels at all anatomical sites than their inactive counterparts.

Conclusion: This Norwegian study of children 15 to 18 years of age found self-reported physical activity to be positively associated with bone mass accrual, with a linear trend among activity categories.

Christoffersen, T., et al. Does the Frequency and Intensity of Physical

Activity in Adolescents Have an Impact on Bone? The Tromso Study, Fit Futures**. BMC Sports Sci Med Rehab.** 2015; 7: 26.

COMPLIANCE WITH REHABILITATION IMPROVES OUTCOME AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

Supervised physical therapy is routinely prescribed after anterior cruciate ligament (ACL) reconstruction. While previous studies have assessed the effects of supervised rehabilitation on quality-of-life and functional outcomes, none have looked at its effect on return to sport. This study examined the effect of compliance with rehabilitation on an athlete's ability to return to sport.

Subjects were 93 recreational athletes with acute ACL tears, referred for surgical reconstruction. After surgery, all patients were referred to physical therapy (PT). All participants were advised to attend 20 PT outpatient appointments, over nine months. At the end of six months, the patients were allowed to return to sport. The number of PT outpatient sessions attended in the first nine months after surgery was determined from the subjects' records.

Follow-up evaluations included Lysholm knee scores, Knee injury and Osteoarthritis Outcome Scores (KOOS) and Short Form-36 Health Survey (SF-36) physical component summary (PCS) and mental component summary (MCS) scores. The patient's ability to return to sport was also documented through self-report. Subjects were considered fully compliant if they attended 15 or more sessions, and noncompliant if they attended fewer than six sessions.

Patients in the fully compliant group earned better scores on the Lysholm ($p<0.001$), KOOS sport/rec ($p=0.021$), KOOS Symptoms subscale ($p=0.040$) and SF-36 PCS ($p=0.012$) ADL subset than did the noncompliant group. Further, subjects in the fully compliant group had significantly greater odds of return to sport (odds ratio 18.5) than did those in the noncompliant group ($p=0.013$).

Conclusion: This study of recreational athletes undergoing anterior cruciate ligament reconstruction found that compliance with a well-designed, progressive, supervised physical therapy program is correlated with improved knee function and a greater chance of return to sport.

Han, F., et al. Increased Compliance with Supervised Rehabilitation Improves Functional Outcome and Return to Sport after Anterior Cruciate Ligament Reconstruction in Recreational Athletes. **Ortho J Sports Med.** 2015, December; 3: 12.

THC/CBD ORAL MUCOSAL SPRAY FOR SPASTICITY

Spasticity is common among patients with Multiple Sclerosis (MS), with a higher prevalence in those with moderate to severe MS. Previous studies have suggested that treatment of MS-related spasticity with an oral mucosal spray containing delta tetrahydrocannabinol (THC) and cannabidiol (CBD) may be effective in reducing spasticity. This study further explored the utility of this medication for moderate to severe MS-related spasticity.

This multicenter, observational, prospective, non-interventional study included patients who had recently been prescribed THC-CBD oral mucosal spray. Patients were excluded if they had other causes of spasticity or cognitive deficits. Data were collected at baseline, and then one and three months after enrollment, using case report forms, physician/patient questionnaires and documentation from medical practice. Outcome measures included changes in the modified Ashworth scale (mAS) and the Numeric Rating Scale (NRS).

Subjects were 322 patients with treatment resistant MS-related spasticity. Of the 203 remaining after the third visit, the mean NRS decreased by 19.1% ($p<0.0001$) and the mAS score from 2.6 to 2.3 points ($p<0.0001$). Improvement of at least 30% (clinical responders) was noted among 24.6%. The mean dose was 6.1 sprays per day. The most common side effects were dizziness, confusion and nausea, experienced by 13% of the participants.

Conclusion: This study of patients with multiple sclerosis-related spasticity found that a THC-CBD oral mucosal spray is effective in reducing spasticity and is well tolerated in everyday use.

Trojano, M., et al. Effectiveness and Tolerability of THC/CBD Oral Mucosal Spray for Multiple Sclerosis Spasticity in Italy: First Data from a Large, Observational Study. **Eur Neurol.** 2015, December; 74(3-4): 178-185.

IMPACT OF COGNITIVE DYSFUNCTION ON SURVIVAL AFTER ENDARTERECTOMY

For patients with high-grade carotid artery stenosis, carotid endarterectomy (CEA) is a common revascularization procedure, performed to reduce the risk of stroke. With this procedure there is some risk of perioperative neurologic injury, including both clinical stroke and early cognitive dysfunction. This study was designed to determine whether early cognitive decline (ECD) is associated with worse long-term survival after CEA, and whether this association differs, depending upon the patient's use of statins.

This study was the *post hoc* analysis of a prospective, observational study of patients undergoing CEA. The participants completed a neuropsychometric battery preoperatively and within 24 hours after CEA surgery. Differences were calculated between the preoperative and postoperative testing scores. Statin use was recorded at the time of enrollment. During follow-up, the dates of all deaths were obtained from the National Death Index (NDI) of the Centers for Disease Control and Prevention.

Of 585 patients undergoing CEA, 336 were taking statins at the time of enrollment. Patients taking statins lived an average of 12.62 years, compared to 11.98 years among those not taking statins ($p=0.02$). Patients without ECD lived longer than did those with ECD ($p=0.06$). Further analysis revealed an association between ECD status and survival among those not taking statins, with no such association among those who were taking statins.

Conclusion: This study of patients undergoing carotid endarterectomy found that cognitive decline, as measured within 24 hours of surgery, is associated with shorter survival, but only among those patients not taking statin medications.

Heyer, E., et al. Impact of Cognitive Dysfunction on Survival in Patients with and without Statin Use following Carotid Endarterectomy. **Neurosurg.** 2015, December; 77(6): 880-887.

TOPICAL MANNITOL AND CAPSAICIN- INDUCED PAIN

Previous studies have demonstrated that topical and injected sugar and sugar-alcohols affect small, peptidergic polymodal nerve fibers, which are associated with neuropathic pain. Among the treatments for neuropathic pain, capsaicin is known to stimulate the transient receptor potential vanilloid type 1 (TRPV1) receptors, although topical application is often found to produce a painful burning sensation. This study investigated the utility of topical mannitol, a metabolically inert sugar-alcohol, to reduce capsaicin-inducted pain.

This randomized, double-blind, placebo-controlled study evaluated 25 adult participants with intact sensation and pain free lips. A small amount of capsaicin 0.75% was applied to both halves of each subject's upper lip. After five minutes, or when the burning sensation reached a self-reported numeric value of eight of 10, the cream was removed. A cream containing mannitol or a placebo cream was then immediately applied to each side of the upper lip. Subjects self-reported a numeric rating scale pain after 10 minutes.

At five minutes after capsaicin application, subjects reported an average numeric rating scale score of 7.8, equivalent on both sides. The participants noted that the side treated with the mannitol cream had faster resolution and maintenance of pain relief than the control side at three to 10 minutes ($p<0.01$).

Conclusion: This study of subjects with capsaicin induced pain found that topical mannitol may be useful in reducing self-reported pain, suggesting that mannitol may affect the TRPV1 pain receptors.

Bertrand, H., et al. Topical Mannitol Reduces Capsaicin-Induced Pain: Results of the Pilot Level, Double-Blind, Randomized Controlled Trial. **PMR**. December, 2015; 7(11): 1111-1117.

DONEPEZIL AND MEMANTINE TREATMENT VERSUS NURSING HOME PLACEMENT

Treatment with cholinesterase inhibitors and memantine have been found to have a positive effect on the disease trajectory of patients with Alzheimer's disease (AD). However, the effect of these medications on the eventual placement of these individuals in nursing homes is not well understood.

This multicenter, randomized, double-blind, placebo-controlled trial included patients with probable or possible, moderate to severe AD who had been prescribed donepezil continuously for at least three months. The first 80 participants were randomized to continue donepezil at 10 mg per day without memantine, to discontinue donepezil without memantine, to discontinue donepezil and start memantine at 20 mg per day or to continue donepezil and start memantine at 20 mg per day. After 52 weeks, treatment was determined by the providing physician. The patients were assessed with the Standardized Mini Mental State Examination (SMMSE) and the caregiver-rated Bristol Activities of Daily Living Scale (BADLS). The place of residence was recorded for a total of three years.

The data revealed that the discontinuation of donepezil was associated with a doubling of the instantaneous risk of placement in a nursing home within 12 months. There was no significant difference in the risk of placement at later follow-up points. Starting memantine treatment had no effect, either singly or combined with donepezil, at any point during the trial.

Conclusion: This study of patients with moderate to severe Alzheimer's disease found that discontinuation of treatment with donepezil results in a significant increase in the risk of nursing home placement during the first year after discontinuation. No effect on nursing home placement was found with the introduction of memantine.

Howard, R., et al. Nursing Home Placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) Trial: Secondary and Post-Hoc Analysis. **Lancet Neurol.** 2015, December; 14 (12): 1171-1181.

ATRIAL FIBRILLATION AND DEMENTIA

While it is known that atrial fibrillation (AF) is more prevalent among people with dementia, the designs of previous studies have precluded conclusions concerning a causal relationship. This study was designed to better understand the association between AF and dementia.

This prospective cohort study evaluated data from the Rotterdam study, a population-based study which began in 1989, enrolling inhabitants 55 years of age or older residing in a defined area of the Netherlands. Atrial fibrillation was assessed with electrocardiography at baseline and at follow-up examinations. Incident dementia was determined using the Diagnostic and Statistical Manual of Mental Disorders and the National Institute of Neurologic And Communicative Disorders And Stroke- Alzheimer's Disease and Related Disorders Association criteria. Cox proportional hazards regression models were used to assess the association between AF and incident dementia among individuals who were dementia free at baseline.

Subjects were 6,514 participants who were dementia free at baseline. Of these 318 (4.9%) had prevalent AF. During follow-up, 723 participants (11.7%) developed incident AF and 15.3% developed incident dementia. Participants with AF had an increased risk of dementia (HR 1.33). Among those with incident AF, 932 (15.0%) developed dementia. The association of both prevalent and incident AF with dementia was strongest among persons younger than the median age of the population. Among the younger participants, the risk of dementia was strongly associated with the duration of AF.

Conclusion: This prospective study found that atrial fibrillation is associated with an increased risk for dementia, with this association strongest for younger participants with a longer duration of atrial fibrillation.

DeBruijn, R., et al Association between Atrial Fibrillation and Dementia in the General Population. **JAMA Neurol.** 2015, November; 72 (11): 1288-1294.

MONOCLONAL ANTIBODY FOR CHRONIC MIGRAINE

The importance of calcitonin gene -related peptide (CGRP) in the pathogenesis of migraine has been well characterized. This study examined the effect of a fully humanized, monoclonal antibody, TEV-48125, that binds to CGRP, as a treatment for chronic migraine.

This double-blind, randomized, double-dummy, placebo-controlled trial compared the efficacy of two doses of TEV-48125, with that of placebo, administered subcutaneously every 28 days for three months. Subjects were adults diagnosed with chronic migraine according to the international classification of headache disorders. The primary efficacy endpoint was the mean change from baseline in the number of headache hours during the third treatment cycle (weeks nine to 12). The secondary endpoint was the mean change from baseline in the number of headache days of at least moderate severity relative to baseline.

Subjects included 89 in the placebo group, 88 in the low-dose group and 87 the high-dose treatment group. The mean changes in the number of headache hours in the third treatment cycle were 59 in the low-dose, 67 in the high-dose and 37 the placebo group, (p=0.0386 and p= 0.0057, respectively).

Conclusion: This study of patients with chronic migraine headaches demonstrated that a monoclonal antibody, binding to a calcitonin-gene related peptide, can reduce migraine headaches.

Bigal, M., et al. Safety, Tolerability and Efficacy of TEV-48125 for Preventive Treatment of Chronic Migraine: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 2B Study. **Lancet Neurol.** 2015, November; 14(11): 1091-1100.

RESIDUAL EFFECTS OF SLEEP MEDICATIONS ON THE ELDERLY

The overall prevalence of insomnia in the Japanese population is estimated to be 17 to 21%, with 45% taking hypnotics. This study evaluated the potential residual effects of three commonly used medications on the physical and cognitive function of healthy, elderly people the day following drug administration.

Subjects were healthy men and women between 60 and 70 years of age who received a standardized, single dose of zolpidem, triazolam, rilmazoafone or a placebo at bedtime. The next day, several tests of psychomotor performance were completed. Those included the Timed Up and Go (TUG) Test, the Functional Reach Test (FRT), the Body Sway Test, the Critical Flicker Fusion Test, the Simple Discrimination Reaction (SDR) Test and the Short-Term Memory Test (STM).

Only 13 subjects reported serious adverse effects or dropped out of the study. On the TUG test, those taking zolpidem had significantly better results than those taking triazolam. For the FRT, those taking zolpidem and rilmazafone had better results than those taking placebo. For the body sway test, those taking rilmazafone did better than those taking the other medications. For the FRT, compared with placebo, those taking zolpidem and rilmazafone had better results as compared with placebo. For the SDR, those taking rilmazafone had significantly better results compared to placebo.

Conclusion: This prospective, randomized, placebo controlled trial suggests that a single dose of zolpidem or triazolam do not have significant, next day, residual effects on healthy, elderly adults. Subjects taking rilmazafone did report decreased next-day alertness, although they did demonstrate improved steadiness of balance, suggesting that this medication may assist in reducing fall risk in early-morning awakenings.

Uemura, S., et al. Residual Effects of Zolpidem, Triazolam, Rilmazafone and Placebo in Healthy Elderly Subjects: A Randomized, Double-Blind Study. **Sleep Med**. 2015, November; 16(11): 1395-1402.

RILONACEPT FOR THE TREATMENT OF SUBACROMIAL BURSITIS

Among patients with subacromial bursitis, studies have demonstrated an increase in the expression of several cytokine genes (TNF, IL-1alpha, IL-1beta and IL-6). This study assessed the efficacy of treatment with a long-acting IL-1 blocking medication, as compared with that of a corticosteroid.

Subjects were 18 years of age or older, all reporting shoulder pain of a minimum of two weeks' duration, with a diagnosis of subacromial bursitis. The participants were randomized to receive either 160 mg of rilonacept or a mixture of 2 mL of 1% lidocaine, 2 mL of 0.5% bupivacaine and 2 mL of triamcinolone acetonide (40 mg/mL). The primary outcome measure was the QuickDASH questionnaire (a shortened version of the Disabilities of the Arm, Shoulder, and Hand (DASH) Outcome Measure), administered four weeks post-injection.

Comparing QuickDASH scores between treatment arms, a significant difference was found between groups, favoring the triamcinolone group, at four weeks post-injection (p=0.004). At four weeks, the triamcinolone group also had superior pain scores compared with the rilonacept group (p=0.044).

Conclusion: This study of patients with subacromial bursitis found that subjects injected with a long-acting interleukin one blocking medication had significant improvement in pain and function, although that improvement was inferior to that of those injected with triamcinolone.

Carroll, M., et al. Rilonacept in the Treatment of Subacromial Bursitis: A Randomized, Noninferiority, Unblinded Study versus Triamcinolone Acetonide. **Joint Bone Spine.** 2015, December; 82(6): 446-450.

PLANTARIS EXCISION FOR ACHILLES TENDINOPATHY

Achilles tendinopathy can be debilitating. Recent studies have reported encouraging results after the release of adhesions surrounding the Achilles tendon and sectioning of the plantaris tendon. This study evaluated the clinical results and time to return to sport following Achilles tendon release, with plantaris excision among athletes with focal medial Achilles tendon pain.

This prospective, consecutive case series included elite athletes who presented with focal, Achilles tendon pain and swelling along the medial edge of the Achilles tendon. All underwent MRI examination confirming paratendinitis. All athletes

had initially failed conservative intervention, and then underwent surgical release of adhesions between the Achilles tendon and the paratendon. The plantaris tendon was identified, released from the medial aspect of the Achilles tendon and transected. Outcomes were assessed with a visual analog scale (VAS) score and the foot and ankle outcome score (FAOS).

Subjects were 32 athletes with a mean age of 27.2 years and a mean follow-up of 22.1 months. Visual analog scale scores for pain improved from 5.8 to 0.8 ($p<0.001$). Significant improvement was also noted in FAOS scores, from a mean of 333 to 449 ($p=0.007$). Following surgery, 69% of the patients were very satisfied, and 22% partially satisfied, with 94% returning to sport at a mean of 10.3 weeks.

Conclusion: This study of elite athletes with noninsertional Achilles tendinopathy found that excision of the plantaris tendon and debridement of the ventral aspect of the Achilles tendon can significantly improve symptoms and return to sport participation.

Calder, J., et al. Plantaris Excision in the Treatment of Noninsertional Achilles Tendinopathy in Elite Athletes. **Br J Sports Med.** 2015, December; 49(23): 1532-1534.

VISION PROBLEMS IN ISCHEMIC STROKE: EFFECTS ON QUALITY-OF-LIFE

While homonymous hemianopia is the most readily recognized vision problem after stroke, other vision problems occur, including eye motility deficits, visual-perceptual difficulties, reduced vision acuity, ptosis and non-homonymous hemianopia visual field deficits. This study evaluated the prevalence of self-reported vision problems among patients with chronic ischemic stroke.

This prospective study included patients with acute cerebral infarction, admitted to a stroke unit between February of 2006 and July of 2008. All participants received a postal questionnaire at least six months after stroke, which included the 15D Questionnaire, EuroQol 5D (EQ-5D), Hospital Anxiety and Depression Scale (HADS), Fatigue Severity Scale (FSS) and Barthel index. Information concerning vision was obtained from question 2 on the 15D Questionnaire, with any response other than normal vision categorized as a vision problem.

Of the 228 patients responding to the questionnaires, 83 reported a vision problem. Vision problems were associated with general health ($p<0.001$), EQ-5D utility scores ($p<0.001$), 15D utility scores ($p<0.001$), HADS scores ($p<0.001$), depression ($p<0.05$) and FSS scores ($p<0.001$).

Conclusion: This study of patients hospitalized with ischemic stroke found that, at long-term follow-up, one in four reported a vision problem, with those problems associated with worse general health, lower health-related quality-of-life and more depression and fatigue.

Sand, K., et al. Vision Problems in Ischaemic Stroke Patients: Effects on Life Quality and Disability. **Euro J Neurol.** 2016, January; 23 Supplement: 1-7.

PROTON PUMP INHIBITORS IN PATIENTS TAKING ANTITHROMBOTICS

After myocardial infarction (MI), antithrombotic treatments are widely used to reduce the risk of thromboembolism. However, this treatment is accompanied by an increased risk of bleeding. This study investigated the effect of proton pump inhibitor (PPI) treatment on the risk of gastrointestinal (GI) bleeding bleed in patients who were post-MI and taking antithrombotics and nonsteroidal anti-inflammatory medications (NSAIDs).

Subjects were 82,955 patients identified in the Danish National Patient Registry between 1997 and 2011, all of whom were 30 years of age or older, and all of whom had survived for at least 30 days after an MI. Medication use was identified through the records of claimant prescriptions of NSAIDs, proton pump inhibitors and antithrombotic therapy. Comorbidities were identified at the time of discharge from the index MI. The primary outcome measure was hospitalization for GI bleeding or death from gastrointestinal ulcer, hematemesis, melena and unspecified gastrointestinal bleeding.

Of the 128,751 patients admitted with a first MI, 64.4% were taking single or dual antithrombotic therapy and met the study criteria. During a mean of 5.1 follow-up years, 3,229 GI bleeds were documented. The crude incidence for a GI bleed for patients not taking PPIs was 2.1 per 100 person years, compared to 1.8 for those taking PPIs. The adjusted risk of bleeding was lower for patients taking PPIs irrespective of NSAID type, PPI type or antithrombotic treatment.

Conclusion: This study of patients hospitalized with a myocardial infarction found that, among those taking antithrombotic medications, the use of a proton pump inhibitor diminishes the risk of gastrointestinal bleeding, regardless of the type of nonsteroidal anti-inflammatory drug or proton pump inhibitor prescribed.

Olsen, A., et al. Impact of Proton Pump Inhibitor Treatment on Gastrointestinal Bleeding Associated with Nonsteroidal Anti-Inflammatory Drug Use among Post-Myocardial Infarction Patients Taking Antithrombotics: Nationwide Study**. Brit Med J.** 2015; 351: h5096.

LEUKOCYTE – REDUCED PLATELET RICH PLASMA FOR SUPRASPINATOUS TENDINOPATHY

Without intervention, the prognosis for patients with symptomatic rotator cuff tears remains poor. Among the current treatment options, platelet rich plasma (PRP) has been suggested, as this substance contains growth factors of interest for tendon regeneration. This study compared the effects of low versus high leukocyte concentrated PRP on mediators of matrix metabolism in diseased supraspinatus tendons.

This laboratory controlled study included tendon biopsy specimens taken from 20, chronically torn supraspinatus tendons of patients ages 60 to 80 years, who were scheduled for rotator cuff surgical repair. Venous blood was taken from healthy, human volunteers distinct from the rotator cuff donor patients. This blood was used to generate low leukocyte platelet rich plasma or high leukocyte platelet rich plasma.

Tendons were categorized into two groups, group 1, with moderate tendinopathy, and group 2 with severe tendinopathy. After four days of culture with the diseased tendon, specific growth factors and cytokine concentrations within the PRP media were measured. Additionally, gene

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expression of anabolic markers, catabolic markers and interleukin-one beta were measured.

In group 1, tendon cultures with low leukocyte PRP had lower concentrations of interleukin one beta ($p<0.01$), as well as increased ratios of interleukin one receptor antagonists to interleukin one beta ($p<0.01$) and collagen type I to collagen type III gene expression than did high leukocyte PRP ($p=0.04$). In group 2 tendons, neither PRP preparation displayed an enhanced matrix synthesis.

Conclusion: This study of patients with degenerative supraspinatus tendinopathy found that, among those with moderately degenerative rotator cuff tendons, low leukocyte PRP supports normal generation of collagen matrix while decreasing pro-inflammatory cytokines more than does high leukocyte PRP.

Cross, J., et al. Leukocyte Reduced Platelet Rich Plasma Normalizes Matrix Metabolism in Torn Human Rotator Cuff Tendons. **Am J Sports Med.** 2015, December; 43(12): 2898-2906.

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