REHAB IN REVIEW

TM

WWW.REHABINREVIEW.COM

Volume 29 Number 3 | Published by Physicians In Physical Medicine and Rehabilitation | March 5, 2021

STEM CELLS FOR MULTIPLE SCLEROSIS

As mesenchymal stem cells (MSCs) have been found to have immunomodulatory and neurotrophic effects, this study explored the effect of MSCs for patients with active or worsening progressive multiple sclerosis (MS).

Subjects were 65 years of age or younger who had experienced treatment failure with at least one line of MS therapy. In the first phase, one group of patients was randomized to receive an intrathecal (IT) infusion of autologous MSCs (IT-aMSCs) and an intravenous (IV) infusion of normal saline (IV-NS). A second group received an IT infusion of NS (IT-NS) and an IV infusion of aMSCs (IV-aMSCs). A third group received only NS for both infusions. After six months, the treatment groups were crossed over. The primary endpoints were the incidence of adverse events and the change in the Expanded Disability Scale (EDSS/Functional Systems scoring).

Data were completed for 48 patients, with a mean age of 47.5 years. Three serious adverse events were recorded, two related to relapses of MS and one due to a respiratory infection, thought to not be related to treatment. Worsening EDSS scores occurred less often in the IT-aMSC group than in the IV-aMSC groups (6.7% and 9.7%, respectively) compared with the sham-treated patients (41.9%). Among the sham-treated patients, 76.7% experienced deterioration in at least one EDSS score, compared to 31% and 27.6% in the MSC-IT and MSC-IV groups ($p = 0.0002$ and $p = 0.0004$, respectively).

Conclusion: This study of patients with progressive multiple sclerosis found that autologous stem cells could improve patient outcomes, with intrathecal delivery superior to intravenous.

Petrou, P., et al. Beneficial Effects of Autologous Mesenchymal Stem Cell Transplantation in Active Progressive Multiple Sclerosis. **Brain.** 2020, December 1; 143: 3574-3588.

SPHENOPALATINE GANGLION NERVE BLOCK FOR MIGRAINE HEADACHE

Headaches are the most common cause of pain in pediatric patients, with chronic pain often resulting in decreased quality of life and decreased participation in school and in social activities. As the sphenopalatine ganglion (SPG) communicates with the parasympathetic autonomic nervous system and pain receptors, a block applied at this ganglion has been successful in reducing headaches in adults. This study analyzed the effect of a SPG block in pediatric patients with refractory migraines.

This retrospective study included patients seen from 2015 to 2018. Those diagnosed with status migrainosus were referred for an intranasal SPG block after failing medical therapy. An intranasal approach was used. After a local anesthetic was introduced, a catheter was advanced to the anterior superior nasal cavity, with 1 mL of 2% lidocaine gel injected at the anterior superior nasal cavity below the floor of the frontal sinus at the pterygopalatine fossa, then repeated for the contralateral nasal cavity. The primary outcome was a ten-point visual analogue pain (VAS) scale.

The mean pre-and post-procedure pain scores were 5.7 and 3.3 ($p<0.0001$), respectively. No significant differences in pain reduction were seen when comparing males with females.

Conclusion: This study of pediatric patients with persistent migraine headaches found that a sphenopalatine ganglion nerve block could be effective for the treatment of acute pain.

Mousa, M., et al. Sphenopalatine Ganglion Nerve Block for the Treatment of Migraine Headaches in the Pediatric Population. **Pain Physician.** 2020; 23: E1 111-E1 116.

SATELLITE CELL APOPTOSIS AFTER ACL RECONSTRUCTION

Protracted atrophy and weakness of the quadriceps muscle are common after anterior cruciate ligament (ACL) injury and/or anterior cruciate ligament reconstruction (ACL-R). The cell responsible for generating myoblasts in postnatal skeletal muscle is the satellite cell (SC). As the number of SCs is reduced after ACL trauma, this study investigated whether apoptosis plays a role.

Subjects were 16 recreational athletes scheduled for ACL-R. Immediately before surgery and after 12 weeks of rehabilitation, biopsies were obtained from the vastus lateralis of the injured leg. From these biopsies were determined SC number, activated SC and apoptotic SC. The SC apoptosis was determined by terminal deoxynucleotidyl transferase-mediated dUTP nick end-labelling (TUNEL) and staining of Pax7. All subjects engaged in guided resistance training.

Twelve weeks after ACL-R, significant decreases were found in the number of SCs ($p < 0.001$). In addition, the number of apoptotic SCs was increased ($p=0.019$). Twelve weeks after ACL-R, approximately 35% of all SCs were apoptotic as compared with approximately one percent before ACL surgery.

Conclusion: This study of recreational athletes undergoing ACL repair found that, after surgery, a significant increase in satellite cell apoptosis was present, which corresponded with a decrease in the number of satellite cells.

Parstorfer, M., et al. Increased Satellite Cell Apoptosis in Vastus Lateralis Muscle after Anterior Cruciate Ligament Reconstruction. **J Rehab Med.** 2021, February; 53(2): 1-10.

IMPACT OF REHABILITATION START TIME

Data concerning the effects of early post-stroke rehabilitation have produced inconsistent results. This study was designed to better understand the association between the time of rehabilitation onset and patient outcome after a stroke.

Data were obtained from the records of adult patients hospitalized for acute stroke between 2012 and 2016. Data included age, gender, primary diagnosis, comorbidities at admission, the Japan Coma Scale score, and the time from admission to the onset of stroke rehabilitation. The primary outcome measure was the modified Rankin scale (mRS) at discharge.

Data were obtained for 140,655 patients with a median age of 70.6 years. Rehabilitation was started on day one for 12.1%, day two for 12.4%, day three for 12.6%, day four for 12.4%, day five for 12.5% and day six or later for 13.0%. The odds ratios (ORs) for a favorable outcome at discharge were similar for those with rehabilitation onset at days one and two. For those with ischemic strokes, this OR decreased with later rehabilitation start dates, with significantly worse discharge mRS scores for those with rehabilitation onset at days three, four, five and six or later ($p<0.001$ for all comparisons). For those with hemorrhagic strokes, compared to onset on day two, significantly worse outcomes were noted for those with rehabilitation onset at day one ($p=0.004$), day three ($p=0.008$) and day six or later ($p=0.005$).

Conclusion: This large Japanese study of patients hospitalized with ischemic or hemorrhagic stroke found better functional outcomes at discharge for ischemic stroke patients who began rehabilitation at day one or two, and for hemorrhagic stroke patients who began on day two.

Otokita, S., et al. Impact of Rehabilitation Start Time on Functional Outcomes After Stroke. **J Rehab Med.** 2021, January; 53(1): 1 -8.

APATHY AND DEPRESSION AFTER STROKE

Evidence suggests that post-stroke depression is associated with an unfavorable outcome. The impact of post-stroke apathy is not clear. This study compared the association between apathy and depression with functional outcome after stroke.

This prospective study included patients with ischemic stroke or transient ischemic attack admitted to the hospital within 48 hours of symptom onset. All were assessed on day eight for depression using the Patient Health Questionnaire (PHQ-9), with scores of 10 or greater indicating greater depression, and for apathy using the Apathy Evaluation Scale (AESC). The participants were then divided into four groups, group one (without greater depressive and apathetic symptoms: A-/D-), group two (only greater apathetic symptoms: A+/D-), group three (only greater depressive symptoms: A-/D+), and group four (both greater apathetic and depressive symptoms: A+/D+). The modified Rankin Scale (mRS) was used to assess poor functional outcomes (mRS score 3-6).

Subjects were 443 patients, of whom 25.3% had greater depressive symptoms and 35.0% had apathetic symptoms. A multivariate analysis revealed that apathetic, but not depressive, symptoms were associated with poor functional outcome at 12-months ($p<0.01$). An adjusted analysis indicated that, compared with group one, group two was at increased risk for an unfavorable functional outcome ($p<0.01$). Twelve-month fatality occurred in 25% of group four, 14% of group two, 8.5% of group three and 4.3% of group one ($p<0.01$).

Conclusion: This prospective study found that early apathetic symptoms occurring with or without depression, but not depression symptoms alone, are associated with an unfavorable prognosis after stroke.

Dziedzic, T., et al. Early Apathetic, but Not Depressive Symptoms, Are Associated with Poor Outcome after Stroke. **Euro J Neurol.** 2021. https://doi:10.1111/ene.14785.

TRANSCRANIAL DIRECT CURRENT STIMULATION PLUS FUNCTIONAL ELECTRICAL STIMULATION FOR GAIT TRAINING FOLLOWING STROKE

Studies have demonstrated that both transcranial direct current stimulation (tDCS) and functional electrical stimulation (FES) can improve mobility and lower extremity strength in patients after a stroke. This study assessed the effect of combining these two modalities.

This prospective trial included 37 patients with a stroke who underwent

conventional rehabilitation, for 40 minutes per day for one week. The patients were randomized to one of three conditions: the FES group to undergo gait training with a WalkAide providing stimulation to the common peroneal nerve; the tDCS group to receive stimulation at 2 mA for 20 minutes a day; the tDCS+FES group to receive both modalities. Outcome measures included the 10 m Walking Test, with accelerometers used to assess gait characteristics. The data were evaluated with three axes, using the unbiased harmonic ratio (HR) to assess smoothness of trunk movement, the autocorrelation coefficient (AC) of gait symmetry, and the root mean square (RMS).

The tDCS+FES group had a greater change in the AC of mediolateral axis acceleration than the FES (p=0.01) or tDCS (p=0.005). Also, the tDCS+FES group had a greater change in the AC of anteroposterior axis acceleration as compared with the FES (p= 0.001) and tDCS (p= 0.005) groups.

Conclusion: This study of patients with chronic stroke found that combining anodal transcranial direct current stimulation and functional electrical stimulation during gait training results in better gait regularity than does either method applied separately.

Mitsutake, T., et al. The Effects of Combining Transcranial Direct Current Stimulation and Gait Training with Functional Electrical Stimulation on Trunk Acceleration during Walking in Patients with Subacute Stroke. **J Stroke Cerebrovas Dis.** 2021, April; 30(4): 105635.

INTENSIVE BLOOD PRESSURE REDUCTION FOR LACUNAR STROKE

The results of the BP arm of the ENCHANTED study did not support a major shift toward intensive blood pressure lowering for patients with mild to moderate acute ischemic stroke (AIS) who received alteplase. However, the authors of that study left open the potential for variability in the effects across pathological subtypes, especially lacunar AIS. This study analyzed the data to determine the effects of intensive BP lowering in thrombolysis-treated patients across lacunar and non-lacunar AIS.

Subjects were 454 patients presenting with a lacunar AIS. The patients were randomized to intensive BP management (target systolic BP [SBP] 130–140 mmHg within 1 h after randomization) or guideline-recommended BP management (SBP < 180 mmHg). Stroke severity was assessed with the National Institute of Health Stroke Scales (NIHSS) at baseline as well as 24 and 72 hours after the start of IV alteplase. Patients were then followed for 90 days to assess functional outcomes and health-related quality of life.

No significant differences were found between groups for intracranial hemorrhage, neurologic deterioration, or death within 24 hours. In addition, there was no significant difference in outcomes between those with lacunar and those with non-lacunar stroke.

Conclusion: This study of patients with lacunar strokes treated with thrombolysis found no benefit in functional outcome with intensive lowering of blood pressure, as compared to guideline-recommended blood pressure management.

Zhou, Z., et al. Intensive Versus Guideline-Recommended Blood Pressure Reduction in Acute Lacunar Stroke with Intravenous Thrombolysis Therapy: The ENCHANTED Trial. **Eur J Neurol.** 2021, March; 28(3): 783–793.

TIMING OF SURGICAL DECOMPRESSION IN ACUTE SPINAL CORD INJURY

For patients with acute traumatic spinal cord injury (SCI), surgical decompression affords an early opportunity to restore spinal cord blood flow, improve perfusion to the penumbra and mitigate secondary injury. However, there is little high-quality evidence to clarify the appropriate timing of surgical decompression.

This literature review included four, prospective, multicentered, spinal cord injury data sets. All participants underwent surgery for progressive neurologic deficits in the setting of ongoing mechanical compression of the spinal cord. The patients were stratified by those who underwent surgery at less than, and those receiving surgery at more than 24 hours. Neurological outcomes were assessed with the American Spinal Injury Association (ASIA) or International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) measures.

Combining outcome scores at one year, those in the early group had better outcomes in total motor scores (p=0.0006), light touch scores (p=0.0021) and pin prick scores (p=0.002), as well as better ASIA Impairment Scale grades at one year after surgery (p=0.0019). When reviewed as a continuous variable, a steep incline was noted in total motor score with increasing time during the first 24 to 36 hours post-injury (p<0.0001). This plateaued after 36 hours.

Conclusion: This pooled analysis of four multicentered spinal cord injury data sets found that patients who underwent surgical decompression of ongoing mechanical compression within 24 hours had better outcomes than did those whose surgery occurred later.

Badhiwala, J., et al. The Influence of Timing of Surgical Decompression for Acute Spinal Cord Injury: A Pooled Analysis of Individual Patient Data. **Lancet Neurol.** 2021; 20: 117-126.

CHRONIC POSTOPERATIVE KNEE PAIN AND INFLAMMATION

Studies have shown that, after total knee replacement (TKR), up to 20% of patients develop chronic, postoperative knee pain. This study evaluated the influence of inflammatory status, as well as physical and psychological factors, among patients with postoperative knee pain five years after total knee replacement (TKR).

Patients who underwent TKR in 2011 were invited to a five-year follow-up. Using a 10 cm visual analog scale (VAS), the subjects were asked to rate their average pain over 24 hours. The subjects were then divided into a high pain group (HPG), with a VAS of three or greater, or a Low Pain Group (LPG) with VAS scores <3. In addition, all were assessed using the PainDETECT Questionnaire (PDQ), the Forgotten Joint Score (FJS), the Oxford Knee Score (OKS) and the Pain Catastrophizing Scale (PCS). Blood was taken to obtain serum high-sensitivity C-reactive protein levels (hs-CRP).

Data were analyzed for 80 patients, with 18 in the LPG and 60 in the HPG. The HPG had significantly higher hs-CRP levels than the LPG (p< 0.001). The HPG also had significantly reduced knee range of motion, higher scores on the PCS and worse scores on the OKS (p<0.001 for all comparisons).

Conclusion: This five-year follow-up study of patients with total knee replacements found that those with

chronic knee pain had elevated levels of serum hs-CRP.

Skrejborg, P., et al. Patients with High Chronic Postoperative Knee Pain 5 Years after Total Knee Replacement Demonstrate Low Grade Inflammation, Impairment of Function and High Levels of Pain Catastrophizing. **Clin J Pain.** 2021, March; 37(3): 161-167.

DISTAL SEMIMEMBRANOSUS AND MEDIAL MENISCUS

Ramp lesions are defined as a longitudinal tear of the peripheral attachment of the posterior horn of the medial meniscus at the meniscocapsular junction. As some have proposed that the semimembranosus tendon is involved in these lesions, this study explored the gross anatomy and the histology of the posterior horn of the medial meniscus and structures inserted on it.

This cadaveric study included donors with a mean age at death of 84 years. For each cadaver, the surgeons harvested a single stable anatomic specimen, including the medial femoral condyle, the medial tibial plateau, the entire medial meniscus, the cruciate ligaments, the joint capsule, and the distal insertion of the semimembranosus tendon, all observed in their entirety. A sagittal slice was cut to examine the distal insertion on the posterior joint capsule and the posterior horn of the medial meniscus.

In all donors, a direct branch of the semimembranosus and a tendinous capsular branch ended behind the posterior horn of the medial meniscus. The capsular branch protruded over the joint capsule, over the meniscotibial ligament below, and the meniscocapsular ligament above. This did not end in the meniscal tissue. The meniscotibial ligament was inserted on the posteroinferior edge of the medial meniscus. The meniscocapsular ligament insertion was on its posterosuperior edge. Histological analysis of this area revealed that this ligament was inserted differently from the insertion previously described in the literature.

Conclusion: This cadaveric study found that the capsular branch of the semimembranosus tendon inserts behind the medial meniscus, while the meniscotibial ligament is inserted on the posteroinferior edge of the medial meniscus.

Cavaignac, E., et al. What is the Relationship between the Distal Semimembranosus Tendon and the Medial Meniscus? A Gross and Microscopic Analysis from the SANTI Study Group. **Am J Sports Med.** 2021, February; 49(2): 459-466.

EDARAVONE DEXBORNEOL VERSUS EDARAVONE ALONE FOR THE TREATMENT OF ACUTE ISCHEMIC STROKE

Edaravone, an antioxidant drug, has been shown to improve acute ischemic stroke (AIS) outcomes through scavenging hydroxyl-, peroxyl- and superoxide-free radicals. Edaravone has been recommended as a treatment for AIS by Chinese and Japanese stroke guidelines. More recently, (+)-borneol, a naturally occurring organic compound, has been found to inhibit the production of inflammatory factors and preserve brain function in preclinical investigations. This phase three trial was designed to compare the effects of edaravone dexborneol with that of edaravone in patients with AIS.

The TASTE trial (Treatment of Acute Ischemic Stroke with Edaravone Dexborneol) is a phase three, randomized, double-blind, comparative study, enrolling patients at 48 centers in China. Subjects were 35 to 80 years of age, presenting with AIS. Participants randomized to an edaravone dexborneol group received edaravone dexborneol IV 37.5 mg/ dose every 12 hours for 14 days. Those randomized to an edaravone group received the same treatment, excluding (+)-borneol. The primary efficacy outcome was the proportion of patients with a favorable outcome, defined as a modified Rankin Scale (mRS) score of less than one.

A favorable outcome was found in 67.18% of the edaravone dexborneol group and in 58.97% of the edaravone group (p=0.004). The two groups had similar incidences of adverse events, serious adverse events, and deaths.

Conclusion: This clinical trial of patients with an acute ischemic stroke found that those who received edaravone dexborneol were more likely to have a good functional outcome than those who received edaravone alone.

Wang, J., et al. Edaravone Dexborneol versus Edaravone Alone for the Treatment of Acute Ischemic Stroke. A Phase III, Randomized, Double-Blind, Comparative Trial. **Stroke.** 2021, March; 52(3): 772-780.

TOCLIZUMAB FOR POLYMYALGIA RHEUMATICA

Polymyalgia rheumatica (PMR) is an inflammatory disorder with cardinal symptoms including inflammatory pain at the shoulder and hip. Treatment often includes oral corticosteroids. As inflammation has a direct impact on bone metabolism, this study assessed the effect on bone density by blocking the interleukin (IL)-6 axis with tocilizumab, an anti-interleukin-6 receptor monoclonal antibody.

Subjects were 20, previously untreated, early PMR patients with a median age of 67 years, and 97 healthy controls. Tocilizumab was given as three eight mg/kg intravenous infusions one month apart. From week 12 (W12) to W24, the subjects received low-dose prednisone (0.15 mg/kg/day). To test whether tocilizumab as a first step, and steroids as a second step, influence bone turnover markers, differences in PINP (marker for bone formation) and CTX-I (marker for bone resorption) levels were tested at the time of the 1st treatment initiation (W0), after the 3rd tocilizumab infusion before steroids were introduced (W12), and at the end of the protocol (W24).

Compared with controls, higher levels of PINP were observed at W12 ($p<0.001$) following tocilizumab introduction. A substantial decrease in CTX-I was noted at W24 after steroid initiation as compared to W12 ($p<10^{-4}$). Compared to baseline, PINP and CTX-I at W12 were strongly correlated, reflecting a more normal bone homeostasis obtained under tocilizumab. Greater changes in PINP were observed in patients whose circulating IL-6 levels decreased after tocilizumab therapy.

Conclusion: This study of patients with polymyalgia rheumatica found that tocilizumab therapy has a positive impact on bone homeostasis, increasing bone turnover through the activation of bone formation and bone resorption blockade.

Alegria, G., et al. Tocilizumab Controls Bone Turnover in Early Polymyalgia Rheumatica. **Joint Bone Spine**. May, 2021; 88(3): 105-117.

EARLY FULL WEIGHT BEARING FOLLOWING SURGICAL REPAIR OF DISTAL FIBULA FRACTURES

The standard of care for displaced ankle fractures in adults is surgical repair. This study examined whether full weight bearing can improve clinical outcomes and shorten disability in patients treated with open reduction internal fixation of ankles.

Patients with distal fibular fractures were surgically treated with either a semi-tubular plate (group one) or a polyaxial locking plate (group two). After surgery, group one received rehabilitation, including partial weight bearing, restricted to 20 kg for six weeks using a medical walking boot, and range of motion out of the walking boot. After six weeks, increased weight bearing was allowed, achieving full weight bearing in eight to ten weeks. For group two partial weight bearing was restricted to 20 kg for three weeks, then advanced to full weight bearing. The subjects were assessed with a visual analog scale (VAS) for pain, range of motion, and lower extremity and ankle function, using the Olerud and Molander Ankle Score (OMAS), the Foot and Ankle Outcome Score (FAOS) and the Karlsson and Peterson Scoring System for Ankle function (KPSS).

Subjects were 45 individuals with a mean age of 43 years. Twenty-five were assigned to group 1 (55.6%), and 20 patients (44.4%) to group 2. Compared to group one, significantly better OMAS scores were noted in group two at six and 12 weeks ($p<0.02$, and $p<0.04$ respectively). Similar findings were noted in KPSS scores. Minor complications were found in 16% of group one and 10% of group two.

Conclusion: This study of patients with distal fibular fractures found that weight bearing at three weeks using a polyaxial locking plate resulted in significantly better clinical outcomes at six and 12 weeks.

Zyskowski, M., et al. Is Early Full Weight Bearing Safe Following Locking Plate ORIF of Distal Fibula Fractures? **BMC Musculoskel Dis**. 2021; 22: 159.

EXTRACORPOREAL SHOCKWAVE THERAPY FOR KNEE OSTEOARTHRITIS

Treatments for osteoarthritis of the knee (KOA) include oral medication, exercise, intra-articular drug injection, and physiotherapy. This study explored the dose-response relationship between treatment doses and the reduction in pain and dysfunction in patients with KOA.

The patients were randomized either to a placebo group or to one of four active treatment groups. These included 0.12 mJ/mm2, lower density (LD) /2,000 impulses (n=19), LD/4,000 impulses (n=18), 0.24 mJ/mm2, higher density (HD) /2,000 impulses (n=19) or HD/4,000 impulses. A placebo group (n=14) received treatment with a minimum positive energy flux density. The primary outcome measure was pain intensity, assessed with a visual analog scale (VAS). The secondary outcome measure was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

At four weeks, all treatment groups demonstrated greater reductions in VAS pain and WOMAC scores as compared with the control group. Also, VAS scores were more improved in the HD group than in the LD group ($p<0.001$), with no difference between the 2,000 and 4,000 impulse groups. For WOMAC scores, compared to the LD group, those in the HD group earned significantly better scores ($p=0.005$). Also, WOMAC scores were better in the 4,000 than in the 2,000 impulses group ($p=0.022$).

Conclusion: This randomized, placebo-controlled trial of patients with osteoarthritis of the knee found that extracorporeal shockwave therapy can improve pain and function, with better pain reduction using higher energy and better WOMAC progression using a higher number of impulses per session.

Zhang, Y., et al. Dose-Related Effects of Radial Extracorporeal Shock Wave Therapy for Knee Osteoarthritis: Randomized, Controlled Trial. **J Rehab Med.** 2021 Jan 13;53 (1):jrm00144. doi: 10.2340/16501977-2782. PMID: 33367924.

TREATMENT OF DIABETIC PERIPHERAL NEUROPATHY

Diabetic peripheral neuropathy (DPN) is the most common and debilitating complication of diabetes. Current treatment standards for DPN management focus on symptomatic relief using both nonpharmacological and pharmacological interventions. This systematic review and network meta-analysis evaluated the relative efficacy and safety of interventions for DPN.

The literature review included randomized, controlled trials of adults with painful DPN. Pharmacologic interventions included pregabalin, gabapentin, lacosamide, lamotrigine, carbamazepine, oxcarbazepine, valproate, oxycodone, amitriptyline, desipramine, imipramine, duloxetine, and venlafaxine. From the trials reviewed, 43 were chosen for this analysis.

Of the 43 trials, 29 reported on the frequency of a 50% or more reduction in pain. Of the multiple comparisons, nortriptyline had the greatest probability of achieving a $\geq$50% pain reduction. This finding was followed by carbamazepine and lamotrigine. Of those that reported a $\geq$30% percent pain reduction, nortriptyline again had the greatest probability of achieving this level of pain reduction. The greatest probability of withdrawal from the research protocol was found among those who received sodium valproate. Withdrawal due to adverse events was most likely among those treated with benztropine.

Conclusion: This systematic review and meta-analysis of studies of treatments for diabetic peripheral neuropathy found that nortriptyline was most likely to produce at least a 50% reduction in pain.

Asrar, M., et al. Relative Efficacy and Safety of Pharmacotherapeutic Interventions for Diabetic Peripheral Neuropathy: A Systematic Review and Bayesian Network Meta-Analysis. **Pain Physician**. 2021, Jan/Feb; 24: E1-E14.

SOCIAL DEPRIVATION AND ONE YEAR STROKE SURVIVAL

Data are inconsistent concerning the impact of social deprivation on poststroke outcome. This study was designed to better understand the impact of social deprivation on patients with first-ever stroke.

Data were obtained from the INDIA (INégalities Sociales et Pronostic des Accidents Vasculaires Cérébraux à DIjon et en Antilles-Guyane) French Multicenter Prospective Cohort Study. Subjects were adult patients admitted for acute stroke. Deprivation was assessed at the individual level using the EPICES (Evaluation de la Précarité et des Inégalités de Santé dans les Centres d'Examen de Santé) score, which measures the social and material dimensions of deprivation. On this scale, scores of 30.17 or greater are considered to represent social deprivation. Other data reviewed

were demographic characteristics, stroke severity, and disability, as measured with the modified Rankin Scale (mRS).

During the study 1,312 consecutive patients with ischemic stroke were included, with a median follow-up of 373 days. Of these, 52% scored >30.17 on the EPICES. The median hospital stay was 11 days for deprived subjects and nine days for non-deprived subjects ($p<0.0001$). The cumulative probabilities of death at one year were 16% in deprived patients and 11% in non-deprived patients. After adjustment for potential determinants of stroke prognosis (age, severity at admission and comorbidities), the risk of death was nearly twice as high in deprived than in non-deprived patients ($p=0.016$).

Conclusion: This study of patients hospitalized with first-ever stroke found that social deprivation is associated with a reduced chance of survival.

Bejot, Y., et al. Social Deprivation and One-Year Survival after Stroke: A Prospective Cohort Study. **Euro J Neurol.** 2021, March; 28(3):800-808.

LONG-TERM DEMENTIA RISK

Data have shown an association between cognitively stimulating activities and a reduced risk of dementia. This study was designed to better understand the associations between adult activity participation and the risk of dementia.

Data were obtained from the Million Women Study, a population-based, prospective study, involving one in four UK women born during 1935 through 1950. Data for cognitive and social activities were added in 2001. The primary exposures included participation in adult education, groups for art, crafts or music, and voluntary work. The main outcome variable was the first mention of dementia in the data system.

Data for 851,307 women were eligible for analysis. Of these, 33% were engaged in at least one of the cognitive or social activities. Among those with no participation in reading, the relative risk (RR) of dementia in the first four years was 3.18, and at five to 10 years was 1.37. This risk fell to near zero after 10 years. In a similar fashion, the RR of dementia was increased in the first four years for those with no participation in adult education (RR 1.72), art/crafts/music (RR 1.37) performing voluntary work (RR 1.27), or for any of the three activities (RR 3.4). The reduced effect over ten years followed the same pattern for all activities.

Conclusion: This prospective study demonstrates that the risk of dementia is greatly reduced in the first five years and moderately reduced in the second five years for those who engage in reading, arts/ crafts/music and/or volunteer activity.

Floud S., et al. Cognitive and Social Activities and Long-Term Dementia Risk: The Prospective, UK, Million Women Study. **Lancet Public Health.** 2021, February 1; 6(2): E116-E123.

CEREBELLUM IMAGING IN MILD COGNITIVE IMPAIRMENT

It is estimated that 15% to 20% of patients with clinically probable Alzheimer's disease (AD) have no significant pathology on amyloid positron emission tomography (PET). How the cerebellum contributes to disease progression in amyloid negative mild cognitive impairment (AN-MCI) has not been well studied. This study investigated the potential relationship between cerebellum volume and the conversion to dementia among patients with AN-MCI.

Subjects were 102, amnestic AN-MCI patients, 50 years of age or older, with no amyloid deposition noted on PET scans. All subjects underwent neuropsychological evaluations, 3T magnetic resonance imaging, including three-dimensional T1 imaging, and PET scans. Of the 102 patients, conversion to dementia occurred in 39 (38%) patients at a median of 22.6 months. Data were compared between those who converted (converters) and those who did not (non-converters).

Neither vascular risk factors nor depression scores differed between the converters and the non-converters. The converter group showed significant bilateral cerebellar gray matter volume loss in the crus I/ II and vermis (IV, crus II and VIIb) compared to the non-converter group ($p<0.001$), with the most prominent differences observed in the right crus I/II area. No statistically significant association was found between cerebellar GM atrophy and neuropsychological test results.

Conclusion: This study of patients with amyloid negative, amnestic, mild cognitive impairment found that those who converted to dementia were more likely to demonstrate volume loss in the cerebellum vermis and crus I/II, independent of neuropsychological test results.

Lee, J., et al. The Cerebellum Could Serve as a Potential Imaging Biomarker of Dementia Conversion in Patients with Amyloid Negative, Amnestic, Mild Cognitive Impairment. **Euro J Neurol.** 2021. https://doi-org.proxy.library.emory.edu/10.1111/ene.14770.

DELAYED INTRACRANIAL HEMORRHAGE AFTER TRAUMA

After a head trauma, the incidence and significance of delayed intracranial hemorrhage (D-ICH) is not well understood. This study was designed to determine the incidence of D-ICH, as well as to determine associations with medications, age, and initial Glasgow Coma Scale scores.

This retrospective study included all head trauma patients who had undergone at least two CTs of the brain (CTBs), with ICH discovered in the second CT after an initial normal CTB.

During the six-year study 19,110 patients presented, of whom 3,360 underwent two or more CTB's. Of those, 653 had an initially normal CTB, among whom six were found to have a D-ICH. None of these required neurosurgeries. There was no univariable association between older age, gender, initial GCS, and D-ICH. Exposure to anti-coagulant medication was associated with lower odds of sustaining a D-ICH.

Conclusion: This study of adult patients presenting to a trauma center with head trauma found that delayed intracranial hemorrhage was not associated with older age, Glasgow Coma Scale scores or antiplatelet medications, with a lower risk found for those taking anticoagulant medications.

Mitra, B., et al. Delayed Intracranial Hemorrhage after Trauma. **Brain Inj.** 2021. DOI: 10.1080/02699052.2021.1887520.

NEUROMOBILIZATION FOR SHOULDER IMPINGEMENT

The shoulder impingement syndrome (SIS) consists of rotator cuff tendinitis and bursitis of the shoulder. There are three theories describing the origin of tendon pain in SIS, including mechanical, vascular,

and neural. This study compared the effects of neuromobilization (NM), added to physiotherapy, on the pain and functional disability of patients with SIS.

Subjects were eighty patients with a history of SIS. All were assessed for pain at baseline and follow-up, using a visual analog scale (VAS) and the University of California at Los Angeles rating scale (UCLA) of functional disability. Routine physiotherapy included pulsed, short-wave diathermy, ultrasound therapy and transcutaneous electrical nerve stimulation. Exercise included shoulder strengthening and stretching, performed for five seconds with 10 repetitions. NM was applied using Butler's recommendations, including neural sliders progressing to neural tensioners.

Data were completed for 68 patients. At the final follow-up, VAS pain scores had improved from 6.95 to 2.15 in the experimental group and from 6.78 to 4.9 in the control group ($p<0.001$). For the secondary outcome, the UCLA score, improvements were similarly more improved in the treatment group than in the control group ($p<0.001$).

Conclusion: This study of patients with shoulder impingement syndrome found that adding neural mobilization to conventional physiotherapy can improve pain and function outcomes as compared with physiotherapy alone.

Akhtar, M., et al. The Effectiveness of Routine Physiotherapy, With and Without Neuromobilization, on Pain and Functional Disability in Patients with Shoulder Impingement Syndrome; A Randomized, Control Clinical Trial. **BMC Musculoskel Disord.** 2020 Nov 21;21(1):770. doi: 10.1186/s12891-020-03787-0.

WHOLE BODY VIBRATION DURING ISOMETRIC CONTRACTIONS

Increments in strength after resistance training result from both neural and structural adaptations. Whole body vibration training (WBVT) has been shown to improve dynamic exercise performance and to improve force-velocity and power-velocity profiles. This study examined the effects of six weeks of WBVT on maximal isometric strength and muscle activity.

The subjects were 30 healthy young adults, randomized to a control group (CG) or a WBVT group. Isometric maximal voluntary contraction (MVC) was performed at 45°, 30°, 15° and -15°, with maximal peak work obtained in each position. The WBVT was administered three times per week for 20-25 minutes per session for six weeks. Before and after this training, the subjects were evaluated for body composition, and ankle plantar flexor strength and with electromyography. Ultrasound was used, with fascicular angle and fascicular length analyzed.

The baseline to follow-up change in isometric MVC was greater in the WBVT than in the CG at -15° ($p=0.01$), 0° ($p=0.05$), 15° ($p=0.05$) and 30° ($p=0.04$). No differences were found between groups in EMG amplitudes or changes in muscle architecture.

Conclusion: This study demonstrated that whole body vibration, applied during isometric strength training, can increase isometric plantarflexion strength, without detectable changes in electrodiagnostic signature, muscle architecture or body composition.

Rubio-Aris, J., et al. Effects of Whole-Body Vibration Training on Calf Muscle Function during Maximal Isometric Voluntary Contraction. **Scand J Med Sci Sport.** 2021.https://doi.org/10.1111/sms.13935.

ABILITY OF SB100B TO PREDICT POSTCONCUSSION SYNDROME IN PEDIATRIC PATIENTS WITH MILD TRAUMATIC BRAIN INJURY

Among children who sustain a mild traumatic brain injury (mTBI), 10 to 30% develop cognitive, physical, and emotional symptoms, referred to as post-concussion syndrome (PCS). While concussion symptoms usually resolve within seven to 10 days, a minority persist for months or even years. Studies of adults have found that transient elevations of levels of S100B correlate with abnormal CT findings. This study assessed the efficacy of this test in predicting postconcussion syndrome in pediatric patients.

Subjects were children, seven to 16 years of age, each presenting with a head trauma with no other complaints. Blood samples were obtained within three hours after the head injury. All were examined with the Rivermead Post-Concussion Syndrome measure. This test was repeated at three months. The participants were then divided according to those with the presence of PCS and those without.

The mean value of S100B protein in serum in 38 patients without signs of PCS was 0.266 μg L^{-1}. Among the 22 patients with signs of PCS, the mean value of S100B protein in serum was 0.845 μg L^{-1}. The mean level of S100B protein in the serum of patients without cranial injury (head CT-) was 0.150 μg L^{-1}. Patients with cranial injury (head CT+) had a mean serum S100B protein level of 0.587 μg L^{-1}. The receiver operating characteristic (ROC) analysis shows that S100B levels differed significantly between patients with and without PCS after TBI ($p = 0.0001$).

Conclusion: This study of pediatric patients with a mild traumatic brain injury, found that S100B protein is a useful neurobiomarker for identifying paediatric patients at risk of post-concussion syndrome.

Kelmendi, F., et al. Ability of S100B To Predict Post-Concussion Syndrome in Pediatric Patients Who Presented to the Emergency Department with Mild Traumatic Brain Injury. **Br J Neurosurg.** 2021. doi: 10.1080/02688697.2021.1878487.

NATURAL HISTORY OF CHARCOT-MARIE-TOOTH TYPE 2A

Charcot-Marie-Tooth Disease, Type 2A, (CMT2A) is the most common axonal form of CMT. As little data exists concerning the natural history of this disease, this study reviewed the relationships between genotype and phenotype and clinical prognosis.

This cross-sectional and longitudinal study included data from the ongoing Inherited Neuropathy Consortium (INC-RDCRN) natural history study of CMT. Subjects were 196 patients diagnosed with autosomal dominant CMT2A (AD-CMT2A) who carried a heterozygous variant in the gene Mitofusin 2 (*MFN2*). Clinical outcome measures were the CMT Neuropathy Score, version 2 (CMTNSv2) and the Rasch Modified CMTNSv2 (CMTNSv2-R). The clinical characteristics of the patients were analyzed after classifying by inheritance pattern, age of onset, variant topology and the biological effect of variants. Inheritance patterns included AD-CMT2A and AR-CMT2A.

Most patients with AD-CMT2A and AR-CMT2A first noticed symptoms in the first two decades of life, usually including walking or

(Continued from page 2)

*Chloe McCloskey, M.D.
Radhika Manne, M.D.
David Quan, M.D.
Univ. of Pennsylvania, Phila, PA

*Austin Marcolina, D.O.
Audrie Chavez, M.D.
Amanda Lindenberg, D.O.
Amanda Ly, M.D.
Maria Lyuksyutova, M.D.
Univ. of TX SW Med Ctr., Dallas, TX

Jacob Boomgaardt, M.D.
Univ. of VA, Charlottesville, VA

*Brian Cervoni-Rosario, M.D.
Univ. of Washington, Seattle, WA

*Bonnie Weigert, M.D.
Y. Fransoua Her, M.D.
Vincent Yaccarino, M.D.
Univ. Of Wisconsin, Madison, WI

balance difficulties. Patients with AR-CMT2A almost always had disease onset and first symptoms in childhood with an average age of onset of 8.06 years. The childhood onset of AD-CMT2A was found to be the most predictive of disease severity, independent of disease duration. The main outcome measures, CMTESv2 and CMTNSv2-R, were significantly related to disease duration ($p<0.001$). The majority of pathogenic mutations were found in the dynamin-GTPase domain of mitofusin-2 (MFN2). The amino acid positions p.Arg94, p.Arg364 and p.Trp740 were the three most common residues for the occurrence of missense variants in MFN2 causing CMT2A. The amino acid position p.Arg94, which is the most common of the three, showed a significant correlation of baseline CMTESv2 with disease duration ($p<0.001$).

Conclusion: This longitudinal study of Charcot-Marie-Tooth Disease, Type IIA, found that the greatest disease severity occurs among those with childhood onset of autosomal dominant CMT2A.

Pipis, M., et al. Natural History of Charcot-Marie-Tooth Disease Type 2A: A Large, International, Multicentre Study. **Brain.** 2020 Dec 1;143 (12):3589-3602.

***Rehab in Review (RIR)* is produced monthly by physicians in the field of Physical Medicine and Rehabilitation (PM&R), with the cooperation and assistance of Emory University School of Medicine, Department of Rehabilitation Medicine. The summaries appearing in this publication are intended as an aid in reviewing the broad base of literature relevant to this field. These summaries are not intended for use as the sole basis for clinical treatment, or as a substitute for the reading of the original research.**

The Emory University School of Medicine designates this journal based activity for a maximum of 3 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity. The Emory University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians. The journals are offered as a CME accredited activity for 3 years from the date of original publication.

***RIR* is affiliated with the Association of Academic Physiatrists, the World Health Organization, and the Chinese and Indian Societies of PM&R and endorsed by the International Society of Physical and Rehabilitation Medicine.**

Private subscriptions are available by email at rehabinreview@aol.com or by fax or phone at (417) 779-9101.

ISSN # 1081-1303

EXPANDING THE FRONTIER OF REHABILITATION SCIENCE IN RESEARCH, TEACHING, AND PATIENT CARE