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KNEE EXTENSOR WEAKNESS AND KNEE OSTEOARTHRITIS

Osteoarthritis (OA) of the knee is the leading cause of pain and disability in older adults. This meta-analysis was designed to better understand the association between knee extensor muscle weakness and the risk of incident symptomatic or radiographic OA of the knee.

A literature review was conducted for prospective and retrospective cohort studies, as well as randomized, controlled trials with at least two years of follow-up. All studies included assessment of knee extensor muscle strength at baseline, as well as structural or symptomatic OA assessments.

Eleven studies were chosen for the meta-analysis. Data from three studies indicated that knee extensor muscle weakness was associated with incident symptomatic OA for both women (OR 1.85) and men (OR 1.43). Data from seven studies found an association between knee extensor muscle weakness and radiographic tibiofibular OA in both women (OR 1.43) and men (OR 1.39).

Conclusion: This meta-analysis found that knee extensor muscle weakness was associated with an increased risk of osteoarthritis of the knee in both men and women.

Øiestad B., et al. Knee Extensor Muscle Weakness is a Risk Factor for the Development of Knee Osteoarthritis: An Updated, Systematic Review and Meta-analysis Including 46,819 Men and Women. **Br J Sports Med.** 2021;0: 1 -8. Doi: 10.1136/Bjsports-2021-104861.

GUILLAIN-BARRE AS A COMPLICATION OF COVID-19

Guillain-Barre Syndrome (GBS) is an inflammatory disease of the peripheral nervous system characterized by a rapid progression of ascending weakness of the limbs. This disorder has been linked to a variety of causative pathogens. In January of 2020, the first case of GBS due to COVID was reported in China. This study reviewed all published cases of post-COVID GBS.

A literature review was completed for papers reporting data of patients with GBS and a probable or confirmed recent COVID-19 diagnosis. This review yielded 1,450 articles, of which 79 papers were included in this systematic review.

Data were available for 99 cases with confirmed COVID-19 infection, with an average age of 56 years. The global distribution of countries with more than five cases was 32 cases in Italy, 16 cases in the United States, 12 cases in Spain, nine cases in Iran, six cases in France, and six cases in the United Kingdom. The average latency period between COVID-19 symptoms and neurologic manifestations was 12.2 days. The most common arboviral symptoms prior to GBS were fever, dry cough, dyspnea, and gastrointestinal symptoms. The most commonly reported neurological signs and symptoms were ascending motor weakness (tetraparesis and paraparesis), diminished deep tendon reflexes, sensory disturbances (paresthesia), sensory loss, and facial palsy. The GBS was complicated by respiratory failure in 30 cases and dysautonomia in 20 cases. The clinical GBS variant that was most common was classical sensorimotor GBS in 64 cases. Of the 77 undergoing EMG, predominant EMG variants of GBS were AIDP (59 cases), followed by AMSAN (10 cases), and AMAN (8 cases). Seventy-two cases received intravenous immunoglobulin (IVIG) therapy, 10 cases were treated with plasmapheresis (PLEX), and seven cases were treated with both IVIG and PLEX.

Conclusion: This systematic review of cases of Guillain-Barre following COVID-19 infection found 99 cases worldwide with classical sensorimotor as the most common type.

Aladawi, M., et al. Guillain-Barre Syndrome as a Complication of COVID-19: A Systematic Review. **Can J Neurol Sci.** 2022, Jan;49(1): 38-48.

ANTIRETROVIRALS AND BODY MASS INDEX

Studies of people living with HIV have suggested that, among those with exposure to integrase strand transfer inhibitors, particularly dolutegravir, certain subpopulations experience weight gain. Given that dolutegravir and tenofovir alafenamide are recommended antiretrovirals in first-line regimens, the effects of these medications on weight gain need better clarity. This study investigated the effects on weight gain among people in the International Cohort Consortium of Infectious Diseases (RESPOND) cohort.

This prospective, multi-cohort collaboration included data from 17, well-established cohorts comprising over 29,000 people living with HIV. Those included in the study had height and weight recorded before the start of the antiretroviral medications. In the primary analysis, “weight gain” was defined as more than a seven percent increase in BMI from before to after treatment initiation.

Of those studied, 53.5% had a more than seven percent increase in BMI. A multivariable analysis found that lower pre-antiretroviral BMI (<18.5 kg/m² *versus* 18.5-24.9 kg/m²), shorter duration on antiretroviral treatment (three to six months *versus* over three years), black ethnicity (compared with white ethnicity) and use of dolutegravir, etravirine, raltegravir and tenofovir alafenamide (compared with lamivudine) were associated with a greater likelihood of more than a seven percent BMI increase.

Conclusion: This large study of patients living with HIV found that, after the onset of antiretroviral medications, over 50% had more than a seven percent increase in body mass index.

Bansi-Matharu, L., et al., Contemporary Antiretrovirals, and

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Body Mass Index: A Prospective Study of the RESPOND Cohort Consortium. **Lancet HIV.** 2021 Nov;8(11): e711-e722. doi: 10.1016/S2352-3018(21)00163-6.

TRANSCRANIAL DIRECT CURRENT STIMULATION FOR OSTEOARTHRITIS AND NEUROTROPHIC FACTOR

While the main symptom of osteoarthritis (OA) is peripheral pain, central sensitization mechanisms are also implicated. Transcranial direct current stimulation (tDCS) has been found to be effective for the management of chronic pain including that due to OA. Convergent evidence suggests that brain-derived neurotrophic factor (BDNF) is a critical determinate of these effects. This study further explored this relationship.

Subjects were adults, ages 50 to 70 years of age, with symptomatic knee OA. The participants were randomized to receive either sham or active tDCS (2 mA intensity) for 20 minutes on five consecutive days. The anode was placed at C3/C4 contralateral to the affected knee. The cathode was placed over the supraorbital (SO) contralateral to the anode (M1-SO montage). The sham condition used the same configuration. Blood draws were scheduled at baseline and on day five to assess levels of BDNF.

Following adjustment for baseline values, higher levels of log-BDNF were found in the sham tDCS group than in the active tDCS group. Elevated levels of BDNF were correlated with higher scores on the Numeric Rating Scale for pain.

Conclusion: This study of patients with osteoarthritis of the knee found that treatment with tDCS lowered levels of BDNF, with further analysis demonstrating a correlation between higher BDNF levels and pain.

Suchting, R., et al. Changes in Brain-Derived Neurotrophic Factor from Active and Sham Transcranial Direct Current Stimulation in Older Adults with Knee Osteoarthritis. **Clin J Pain.** 2021, December; 37(12): 898-903.

SUSTAINED ACOUSTIC MEDICINE FOR MUSCULOSKELETAL INJURY

In March of 2020, the FDA approved sustained acoustic medicine (SAM) for prescription home use to treat various musculoskeletal injuries. This treatment utilizes high-frequency, low-intensity continuous ultrasound at 3 MHz with 0.132 mW/cm2 intensity delivering 18,720 J over four hours of treatment. This meta-analysis was designed to summarize the clinical effects of this treatment for musculoskeletal injury.

A literature search was completed for studies of adults with musculoskeletal injuries and related pain, treated with SAM. From the search, 13 clinical studies were selected. Subjects were 67 patients with neck and back myofascial pain/injury, 156 with moderate to severe knee pain with confirmed osteoarthritis and 149 with generalized soft-tissue injury of the elbow, shoulder back and ankle.

For upper neck, back and shoulder conditions, the meta-analysis demonstrated that, compared with placebo, SAM treatment resulted in improvement in pain ($p = 0.005$) and health improvement ($p = 0.0001$). For those with knee pain, compared with placebo, SAM resulted in significant reductions in pain ($p < 0.00001$). For soft tissue injuries, compared with placebo, SAM resulted in tissue heating and tissue recovery, improved function, and reduction of pain.

Conclusion: This systematic review and meta-analysis found that sustained acoustic medicine can provide tissue healing, improve pain, and improve function.

Winkler, S., et al. Sustained Acoustic Medicine for the Treatment of Musculoskeletal Injuries: A Systematic Review and Meta-Analysis. **BMC Sports Sci Med Rehabil**. 2021. doi.org/10.1186/s13102-021-00383-0.

INTERMITTENT VERSUS CONTINUOUS BLOOD FLOW RESTRICTION

The American College of Sports Medicine recommends the use of low-dose exercise, equivalent to 60 to 70% of the one repetition maximum, for improving muscle strength. Among those with painful joints, this level may be difficult to attain. Lighter intensities, augmented by blood flow restriction (BFR), have been studied as an alternative. This systematic review and meta-analysis was designed to better understand whether intermittent deflation of the cuff during rest periods (iBFR) could improve tolerance of the exercise, as compared to cuffs which were inflated continuously (cBFR).

A literature was reviewed for randomized, controlled trials comparing cBFR with iBFR among

adult subjects. The initial search yielded 350 citations, of which nine were chosen for inclusion. All participants were 18 years of age or older with no musculoskeletal complaints. Perceived exertion was assessed during each trial with a Borg scale, an OMNI perceived exertion scale for resistance exercise and a visual analogue scale.

For perceived exertion, most studies showed slightly better scores for the iBFR group, although no significant difference was found (p=0.073). Similar findings were noted for improvement in maximum dynamic strength, as the gains favored the iBFR group in all exercises, although the between-group difference did not reach significance. For isometric strength gained, no significant difference was found between the two groups.

Conclusion: This literature review and meta-analysis found that perceived discomfort did not differ between those engaged in blood flow restriction exercises with the cuff inflated continuously versus those who deflated the cuff between sets.

Sinclair, P., et al. Tolerance to Intermittent versus Continuous Blood Flow Restriction Training: A Meta-Analysis. **Int J Sports Med**. 2022, Jan;43(1):3-10.

REHABILITATION IN OLDER PATIENTS HOSPITALIZED WITH ACUTE HEART FAILURE AND DIABETES

Over 40% of patients hospitalized with acute decompensated heart failure in the United States, have comorbid diabetes mellitus. The Rehabilitation Therapy in Older Acute Heart Failure patients (REHAB-HF) targeting patients hospitalized for acute decompensated heart failure, found that an early, transitional, tailored, progressive rehabilitation intervention that included multiple physical-function domains resulted in greater improvement in physical function than usual care. This study assessed the efficacy of the REHAB-HF in patients with diabetes.

This multisite, randomized, single-blind, controlled trial included 349 patients hospitalized with acute decompensated heart failure. All participants were independent, ambulatory, and expected to be discharged to home. Those randomized to a treatment group received one-hour sessions, three times per week for 12 weeks, focusing on strength, balance, mobility, and endurance. Non-intervention days were complemented by home exercise with low intensity walking and strengthening. After 12 weeks, participants were transitioned to a maintenance phase for four to six months with individualized exercise prescriptions. Assessments were made by phone every two weeks to six months. The primary endpoint was the Short Physical Performance Battery (SPPB).

Of the 349 patients in the REHAB-HF study, 186 had diabetes. Those with diabetes had worse baseline SPPB scores than did the non-diabetic patients. Those with diabetes had greater improvement than controls at three months on the SPPB (p<0.001), balance scores (p=0.004), gait speed (p=0.004), chair rise scores (p=0.001) and quality of life (p=0.033). No significant difference was seen between the diabetic and non-diabetic subjects in gains measured at six months.

Murray, E., Physical Rehabilitation in Older Patients Hospitalized with Acute Heart Failure and Diabetes: Insights from REHAB-HF. **Am J Med.** 2022, January;135(1):82-90.

CANNABIS OR CANNABINOIDS FOR PAIN

Chronic pain affects 20% of the population and is associated with physical and emotional impairment, disability, and reduced quality of life. Guidelines concerning the use of cannabinoids for pain have been inconsistent. This literature review was designed to better understand the literature concerning the use of cannabinoids for pain.

Studies included were randomized, controlled trials with at least 20 chronic pain subjects. From this search, 32 studies were selected, including 5,174 patients.

Compared with placebo, non-inhaled medical cannabis resulted in a small increase in the proportion of patients experiencing at least a 30% reduction in pain (relative risk (RR) 1.21). Medical cannabis, when taken orally, improved sleep quality, but not emotional functioning.

Conclusion: This literature review and meta-analysis found that, compared to placebo, non-inhaled medical cannabis or cannabinoids result in a small increase in the proportion of patients who experience an important improvement in pain relief.

Wang, L., et al., Medical Cannabis or Cannabinoids for Chronic Non-Cancer and Cancer-Related Pain: A Systematic Review and Meta-analysis of Randomized, Clinical Trials. **BMJ.** 2021, September 8; 373: n1034.

MORBIDITY AND MORTALITY OF SURGERY IN GERIATRIC TRAUMATIC BRAIN INJURY

There is significant variability in the management of geriatric patients with traumatic brain injury (TBI). This study investigated the impact of a neurological intervention on complications, discharge destination and mortality in geriatric patients undergoing surgical intervention for TBI.

Data were obtained from the National Sample Program of the National Trauma Databank for patients seen between 2003 and 2016. Data were extracted for 127,129 patients 80 years of age or older, including medical diagnoses, mortality, hospital length of stay, number of ventilator days and hospital discharge location. Those who underwent intracranial surgery were compared to those who did not.

The overall incidence of inpatient mortality was 10.6%, with increased mortality noted among those undergoing surgical intervention. A multivariate analysis revealed that surgical intervention was not independently associated with increased mortality. However, surgical intervention was associated with a reduced likelihood of discharge to home (p<0.001), a 5.3-day average increase in hospital length of stay (p<0.001), a 3.19-day average increase in ICU length of stay and an increase in days on a ventilator (p<0.001).

Conclusion: This retrospective study of patients 80 years of age or older with traumatic brain injury found that surgical treatment was associated with increased complications and length of stay as well as a reduced likelihood of discharge to home.

Haddad, T., al. The Morbidity and Mortality of Surgery for Traumatic Brain Injury in Geriatric Patients: A Study of over 100,000 Patient Cases. **Neurosurg.** 2021, December; 89 (6): 1062-1070.

TRANSCRANIAL MAGNETIC STIMULATION FOR NEUROPATHIC PAIN

Repetitive transcranial magnetic stimulation (rTMS) has been used to address chronic pain, with the best efficacy achieved when M1 is stimulated at high frequency,

contralateral to the maximal area of pain. This study assessed the efficacy and safety of TMS delivered to the M1 contralateral to the pain or the left dorsolateral prefrontal cortex in patients with chronic peripheral neuropathic pain.

Subjects were between 18 and 75 years of age with pain for at least six months at four or greater on a 10-point Numerical Rating Scale score. All fulfilled the criteria for probable or definite peripheral neuropathic pain. The participants were randomized to receive a sham treatment or active treatment using rTMS, once per day for five consecutive workdays. This was followed by a maintenance period of one session per week for three weeks, and then one session every two weeks for six weeks and one session every three weeks for 12 weeks. Active or sham-rTMS (of M1 or DLPFC-rTMS) was delivered, with each session consisting of 30 trains, delivered at 10 Hz for 10 seconds (100 pulses/train) with 20-second inter-train interval, resulting in 3,000 pulses per session for a total duration of 15 minutes. The primary treatment outcome variable was the change from baseline in average pain intensity.

Data were completed for 152 patients. Compared with sham rTMS, M1-rTMS was more effective for pain reduction (p=0.04). At 19 weeks, the average change in pain intensity was -1.4 for the M1-rTMS group, -0.6 for the DLPFC-rTMS group and -0.4 for the sham group. The difference between M1-rTMS and sham-rTMS increased after repeated rTMS sessions. Secondary outcome measures related to affect, mood or quality of life did not differ among M1-RTMS, DLPFC-rTMS and sham-rTMS.

Conclusion: This study of patients with chronic, peripheral neuropathic pain found that repetitive transcranial magnetic stimulation with the anode placed at M1 could significantly reduce pain.

Attal, N., et al. Repetitive Transcranial Magnetic Stimulation for Neuropathic Pain: A Randomized, Multicenter Sham-Controlled Trial**. Brain.** 2021, November; 144 (11): 3328:3339.

CAPSIATE SUPPLEMENTATION AND MAXIMAL VOLUNTARY CONTRACTION

Capsaicin (8-methyl-N-vanillyl-trans-6-nonenamide) is a pungent compound found mainly in red peppers and other spicy food. Capsiate (CAP) is a non-pungent compound extracted from the sweet pepper fruit "CH-19 Sweet". As previous studies have demonstrated that CAP can activate the TRPV1 in skeletal muscle, this study assessed the effect of CAP supplementation on isometric knee strength.

This randomized, double-blind, crossover study included 13 men with a mean age of 25.2 years. Baseline data included anthropometric, dietary, and maximal isometric strength assessments. Subjects were randomized to a placebo or a CAP condition, to receive six mg of CAP or placebo 45 minutes before exercise. All participants performed five, 10-second knee extension maximal isometric contractions (MVIC), interspaced by 45 seconds. The peak force of MVIC was determined. The mean force was determined as the mean of force values between one and 8.99 seconds. The minimum force was determined as the mean of 100 ms around the lowest force value. The area under the curve (AUC) of force values was calculated for each set of MVIC. The fatigue index of each MVIC was expressed as a percentage and calculated by subtracting the peak force from the minimum force, divided by the peak force, and multiplied by 100 (a higher value indicates greater fatigue development and a value of 0 indicates that no fatigue has occurred).

Higher values were found in the CAP group for peak force (p=0.02), fatigue index (p=0.041), and area under the curve (p=0.04) compared to placebo.

Conclusion: This study of young, healthy men found that supplementation with six mg of capsiate, 45 minutes before exercise, could improve overall peak force and reduce fatigue.

Gomes, W., et al., Effects of Capsiate Supplementation on Maximal Voluntary Contraction in Healthy Men. **Int J Sports Med**. 2021; 10.1055/a-1502-6563.

PLYOMETRIC TRAINING IN NORMOBARIC HYPOXIA

While traditional Live High-Train High (LHTH) or Live High-Train Low (LHTL) methods are popular with athletes, both require prolonged exposure at moderate to high altitude. With new technology, athletes can now simulate altitude training, known as Live Low-Train High. This study was designed to discover whether plyometric training in normobaric hypoxia can improve sea level sprint and jump performance.

Subjects were 23 male students with an average age of 20.4 years who had not undergone plyometric exercise in the last six months and did not regularly undertake physical activities except for the curriculum of their schools. The participants were divided into three groups: Plyometric training in hypoxia (PTH), plyometric training in normoxia (PTN) and a control group (C). The training occurred in three sessions per week for eight weeks, with at least one day rest between sessions, incorporating three to four plyometric exercises per session.

The PTH group performed the plyometric training under normobaric hypoxic conditions (at approximately 3536 m or FIO2 of approximately 0.135) using a face mask attached to a portable hypoxic generator. The PTN group performed the same training program in normoxic conditions without a face mask. Before (within 15 sec) and immediately after (within 15 sec) each exercise bout, oxygen saturation and heart rate were measured with a pulse oximeter.

An ANOVA revealed that, compared to PTN and C, the PTH group realized significantly better gains in countermovement jump (CMJ), ($p<0.001$ and $p=0.004$, respectively), squat jump, ($p<0.001$ and $p=0.007$, respectively), drop jump (DJ), ($p=0.19$ and $p=0.012$, respectively) and sprint performance ($p=0.005$ and $p=0.45$, respectively).

Conclusion: This study of untrained young males found that plyometric training in normobaric hypoxic conditions improved jump performance better than those who performed plyometric training in normoxic conditions.

Coskun, B., et al., Plyometric Training in Normobaric Hypoxia Improves Jump Performance. **Int J Sports Med.** 2021, Dec 8. doi: 10.1055/a-1656-9677. Epub ahead of print.

INTERVAL TRAINING IN OVERWEIGHT ADOLESCENT FEMALES

The prevalence of obesity has nearly tripled since 1975. Hypertrophic fat tissue resulting from obesity has led to increased levels of inflammation, with excessive release of pro-inflammatory cytokines. Regular physical activity has been considered a nonpharmacologic therapy to treat obesity and to reduce chronic low-level inflammation. This study assessed the effect of interval training for adolescent females.

The subjects were 43 overweight/ obese female adolescents, randomly assigned to one of three groups: a moderate intensity interval training (MIIT) group, a high intensity interval training (HIIT) group and a non-intervention control (CG) group. The HIIT group underwent six to eight repetitions of 30 second bouts of running at 100 to 110 % of maximal aerobic speed (MAS) with 30 seconds of active recovery at 50% of MAS between bouts. This was repeated after four minutes of passive recovery. The MIIT group performed the same sequence of exercise at 70-80% of MAS. At baseline all underwent anthropometric measurements, aerobic capacity assessment and measurement of selected hematologic and inflammatory markers. The Spartacus test was performed to measure speed associated with $V0_{2peak}$ [maximum aerobic speed (MAS)] before and after 12 weeks of training.

The HIIT group realized a 6.82% reduction in body mass (p=0.009), a 15.2% reduction in body mass index Z score(p=0.011), a 4.8% reduction in body fat (p=0.002) and significant reductions in waist circumference (p=0.002), with a 16 1% increase in MAS (p<0.001), heart rate maximum (p=0.003), and systolic blood pressure(p=0.001). The MIIT group realized significant changes only in body mass (-1.51%; p=0.025). A post-hoc analysis revealed significantly greater reductions in CRP in favor of the HIIT group (p=0.004).

Conclusion: This study of overweight, adolescent females found that high intensity interval training is superior to moderate intensity interval training for body composition and aerobic fitness, as well as reduced levels of CRP.

Abassi, W., et al. Interval Training with Different Intensities in Overweight/Obese, Adolescent Females. **Int J Sports Med**. 2021. 10.1055/a-1648-4653.

AIRFLOW RESTRICTION MASK AND CENTRAL FATIGUE

High-intensity interval exercise (HIIE) has been widely used as a time-efficient approach to improve endurance performance. This training method has recently been combined with an airflow restriction mask (ARM) as a means to increase respiratory muscle work by adding external breathing resistance. This study assessed the effect of wearing an ARM on alterations in SpO2, HR, blood pH, plasma lactate concentration, dyspnea, dyspnea, the physical sensation of effort (P-RPE), and Task Effort and Awareness (TEA).

Subjects were 14 healthy men who underwent two sessions of HIIE involving four-minute exercise sessions at 90% heart rate maximum HRmax, with a three-minute recovery period, repeated for a total of four bouts of exercise. The three-minute recovery occurred at 70% of the maximum heart rate without an airflow restriction mask. Subjects were assessed for dyspnea, physical sensation effort, blood pH and plasma lactate concentration, peripheral oxygen saturation and heart rate, electromyography muscle activity recording, and neuromuscular function assessment. Neuromuscular fatigue was quantified as changes in maximal voluntary contraction (MVC), voluntary activation (VA, central fatigue), and potentialized evoked twitch force at 100, 10, and 1 Hz (peripheral fatigue).

The maximum voluntary contraction (MVC) decreased from pre- to post-HIIE in both the control and ARM conditions (all, p<0.001). However, the degree of MVC reduction was greater (p=0.05) in the ARM (−28%) than in the Control condition (−20%). A greater decline was found in the ARM group, central fatigue (p<0.05) but not in peripheral fatigue.

Conclusion: This study of subjects undergoing high-intensity interval training found that wearing an ARM exacerbated perceptual and physiological disturbance. This was accompanied by greater central fatigue did not affect peripheral fatigue.

DaSilva, K., et al. Airflow Restriction Mask Induces Greater Central Fatigue after a Non-Exhaustive, High-Intensity, Interval Exercise. **Scand J Med Sci Sports.** 2021, Nov 17. DOI: 10.1111/sms.14099. Online ahead of print.

ANTI-RETROVIRAL TREATMENT AND BLOOD BRAIN BARRIER INTEGRITY

The human immunodeficiency virus- 1 (HIV-1) invades the central nervous system early. In the absence of antiretroviral therapy (ART), this phenomenon evolves into chronic infection and inflammation, leading to disruption of the blood brain barrier (BBB). As an increased level of neopterin in cerebrospinal fluid (CSF) is associated with impairment of the BBB, this study examined the effect of ART on these levels.

This retrospective, longitudinal study analyzed archived cerebrospinal fluid (CSF) samples from HIV-infected adults before and after the introduction of ART. Of the 159 HIV-infected participants, 82 were neuro-asymptomatic and 77 had HIV-associated dementia (HAD). The untreated were diagnosed as having HAD. All neuro-asymptomatic individuals (82/82), and 10/77 individuals with HAD, were followed for a median of 758 days.

Untreated individuals with HAD had significantly higher CSF HIV RNA ($p < 0.0001$), albumin ratio ($p < 0.0001$), CSF neopterin ($p < 0.0001$), and CSF NfL ($p < 0.0001$), and significantly lower CD4+ T-cell count ($p < 0.0001$) and CD4 nadir ($p < 0.0001$), compared to neuro-asymptomatic participants. Early after the initiation of ART, CSF neopterin had fallen, significant at both six months and three years ($p<0.001$ $p<0.001$ respectively). At the same intervals significant reductions were noted in CSF levels of HIV RNA ($p < 0.001$, $p < 0.001$ respectively), β2-microglobulin ($p < 0.001$, $p < 0.001$ respectively), WBC ($p < 0.001$, $p < 0.001$ respectively), and NfL ($p < 0.01$, $p < 0.001$ respectively).

Conclusion: This study found that blood brain barrier integrity, improved after the introduction of antiretroviral therapy, in both asymptomatic individuals as well as those with HIV-Associated Dementia.

Anesten, B., et al., Effect of Antiretroviral Treatment on Blood-Brain Barrier Integrity in HIV-1 Infection. **BMC Neurol**. 494 (2021). https://doi.org/10.1186/s12883-021-02527-8.

MINOCYCLINE REDUCES COGNITIVE IMPAIRMENT IN METHAMPHETAMINE USERS

Methamphetamine is the second most commonly used illicit drug in the world. Chronic methamphetamine use is associated with psychosis and cognitive impairments. As glial cells play an important role in ion homeostasis, neuromodulation, neurotransmitter turnover in neurodegenerative diseases, this study evaluated the effect of minocycline, a glial cell modulator, on the cognitive and psychotic effects of methamphetamine.

Subjects were five male, treatment-resistant, chronic methamphetamine users who were experiencing cognitive impairments and drug-related psychotic symptoms. The subjects were assessed with the Positive and

Negative Syndrome Scale (PANSS) of psychotic symptoms, the Wisconsin Card Sorting Test (WCST) of cognitive function, and the Wechsler Memory Scale-Fourth Edition (WMS-IV). The subjects then received minocycline, 20 mg, for eight weeks, with assessments at baseline and weeks two, four, and eight.

At the two-month follow-up, the mean score on the PANSS improved by 21.6%. The PANSS scores improved from a mean of 92.4 at baseline to 74 at week two, and 72.8 at week eight. Improvements were also noted for scores on the WMS-IV, with auditory memory improving by 24.3% and visual memory improving by 18%.

Conclusion: This study of treatment-resistant methamphetamine users found that minocycline could improve the cognitive and psychotic symptoms of these patients.

Alavi, S. et al., Successful Use of Minocycline for the Treatment of Methamphetamine -Induced Psychosis and Cognitive Impairments: An Open-Label Case Series. **Clin Neuropharm**. 2021, July/August; 44 (4): 126-131.

FREMANEZUMAB FOR MIGRAINE SYMPTOMS AND RESOURCE UTILIZATION

Migraine is considered the second leading cause of years lived with disability worldwide. Fremanezumab is a fully humanized monoclonal antibody that selectively targets calcitonin gene-related peptide (CGRP), a neuropeptide implicated in the pathophysiology of migraine. This study assessed patient-reported migraine symptoms before and after treatment initiation with fremanezumab.

This retrospective study extracted data in the Midwest component of EMRClaims+®, an integrated health services database for patients 18 years of age or older who were administered fremanezumab. Data abstracted included demographics, as well as clinical activity, including patient-reported headache frequency, intensity, and healthcare utilization.

Data were analyzed for 172 patients with an average age of 46 years, of whom 84% were female. The mean number of headache days per month was reduced from 22.24 days during the baseline period to 8.24 after fremanezumab initiation. The percentage of patients with any inpatient hospitalization remained stable between baseline and post-treatment. The mean number of ER visits per month decreased from 0.72 before treatment to 0.54 after treatment initiation.

Conclusion: This retrospective study of patients with migraine treated with fremanezumab found that, after initiating treatment, 84% of patients reported a decrease in headache frequency or symptoms, with an overall 63% decrease in the average number of headache days per month.

McAllister, P., et al. Real-World Impact of Fremanezumab on Migraine Symptoms and Resource Utilization in the United States. **J Headache Pain.** 2021; 22: 156.

CEREBRAL VENOUS SINUS THROMBOSIS WITH THROMBOCYTOPENIA AFTER COVID VACCINATION

Since March of 2021, cases of cerebral venous sinus thrombosis with thrombocytopenia (CVST) after COVID-19 vaccination have been reported. As the underlying pathophysiology of the anti-platelet factor 4 antibody-induced platelet activation resembled an auto-immune variant of heparin-induced thrombocytopenia [vaccine induced immune thrombotic thrombocytopenia (VITT)], specific treatment recommendations were proposed. These included the use of non-heparin-based anticoagulants, the use of intravenous immunoglobulin as a first-line treatment, and avoidance of platelet transfusion. This study reviewed the effects of this modified intervention.

Using EudraVigilance, a passive pharmacovigilance system, data were collected on all suspected adverse events reported to EudraVigilance until 13 June 2021, for the four available SARS-CoV-2. Cases with CVST onset up to and including March 28, 2021, were compared to those with onset after March 28, 2021, the date that the first paper on VITT was published.

From the database, 270 cases of CVST with thrombocytopenia within 28 days of SARS-CoV-2 vaccination were identified. Of these, 266 (99%) occurred after vaccination with an adenoviral vector-based vaccine, with all but three occurring after the first vaccination. Overall mortality was 31%. In the cases with onset before March 28, 2021, mortality was 47/99 (47%) compared to 36/167 (22%) in cases with onset after March 28, 2021 ($p<0.001$).

Conclusion: This study of cases of cerebral venous sinus thrombosis with thrombocytopenia occurring after a COVID-19 vaccine found that mortality has fallen from 47% to 22% after the introduction of specific treatment recommendations.

Van De Munckhof, A., et al. Declining Mortality of Cerebral Venous Sinus Thrombosis with Thrombocytopenia after SARS-Cov-2 Vaccination. **Euro J Neurol**. 2022, January; 29(1): 339-344.

DISRUPTED HIPPOCAMPAL STRUCTURAL NETWORKS AND IMPAIRED MEMORY IN SUBTYPES OF MILD COGNITIVE IMPAIRMENT

The anterior hippocampus (aHC) and posterior hippocampus (pHC) are two key areas of the brain involved in verbal memory and spatial memory, respectively. This study investigated the effect of these networks, among patients with amnestic mild cognitive impairment (aMCI) and non-amnestic MCI (naMCI).

Subjects were 990, right-handed, native Chinese adults, between 50 and 80 years of age. All were engaged in the Beijing Aging Brain Rejuvenation Initiative, an ongoing longitudinal study examining the brain and cognitive decline in an elderly community-dwelling sample. Through a series of neuropsychological tests, subjects diagnosed with MCI were further classified as aMCI or naMCI. Magnetic resonance imaging (MRI) was completed for all subjects, with partial least squares (PLS) analysis used to determine the patterns of cerebellum disruption. The structural covariance of the hippocampus was computed in two PLS analyses, both with the anterior hippocampus (aHC) and posterior hippocampus (pHC), as the seed regions, to see how these patterns potentially differ or are similar between normal controls (NCs), aMCI and naMCI. The gray matter (GM) volumes in patients with aMCI were smaller than those in the NC group in both the aHC and the pHC. There was no difference between the NC group and naMCI group. Three aHC and pHC structural covariance network patterns emerged. These were the age pattern, the specific aMCI pattern, and the spatial memory pattern. Of the three, the aMCI patients had more extensive and severe damage which correlated with a greater decline in verbal memory, mainly characterized by the aHC network.

Conclusion: This large study of elderly Chinese patients found three specific patterns of hippocampal disruption in patients with mild cognitive impairment.

Du, C., et al. Disrupted Anterior and Posterior Hippocampal Structural Networks Correlate with Impaired Verbal Memory and Spatial Memory

in Different Subtypes of Mild Cognitive Impairment. **Euro J Neurol.** 2021, December; 28(12): 3955-3964.

ATOGEPANT FOR MIGRAINE PREVENTION

Monoclonal antibodies that target calcitonin gene-related peptide (CGRP) have been introduced to reduce the onset of migraines. Atogepant is an orally available CGRP with an elimination half-life of 11 hours. This study assessed the efficacy of this medication for preventing migraines in patients with episodic migraine.

This multicenter, double-blind, placebo-controlled trial included patients with episodic migraine, randomized to receive a placebo or atogepant, dosed at 10 mg, 30 mg, or 60 mg. The patients were seen at baseline and then at weeks two, four, six, eight, and 12. This final visit occurred at week 16, four weeks after the end of the treatment. The primary efficacy endpoint was the change from baseline in the mean number of migraine days per month across the 12-week treatment period.

A total of 2,270 persons were screened. The mean number of migraine days per month was reduced by 3.7 with 10 mg, 3.9 with 30 mg and 4.2 with 60 mg treatment, and 2.5 with placebo ($p<0.001$ for all comparisons with placebo). A reduction of 50% or more in the three -month average of migraine days per month occurred in 55 .6% of those in the 10 mg group, 58.7% in the 30 mg group, 60.8% of those in the 60 mg group, and 29% of those in the placebo group ($p<0.001$ for all, compared with placebo).

Conclusion: This study of patients with episodic migraine headaches found that oral atogepant once per day could significantly reduce the number of migraine days and headache days.

Ailani, J., et al. Atogepant for the Preventative Treatment of Migraine. **N Engl J Med.** 2021, Aug 19; 385(8): 695-706.

AQUATIC PROPRIOCEPTIVE TRAINING AFTER ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

Anterior cruciate ligament (ACL) reconstruction is a common procedure designed to improve the mechanical stability of the knee joint and regain function. It is known that, after ACL injuries, information received by the central nervous system is distorted, leading to clinical proprioceptive deficits and functional instability in most patients. This study assessed the effectiveness of aquatic proprioceptive training, added to conventional land-based rehabilitation, following ACL reconstruction.

Subjects were 38 males who had undergone recent ACL reconstructive surgery. The subjects were randomized to receive conventional therapy (CT) or CT plus hydrotherapy (HT). Both groups received an accelerated, land-based rehabilitation protocol for seven weeks starting one -day post-surgery. In addition, the HT group participated in 12 sessions of aquatic proprioceptive training. The HT group trained in water at a depth between the waist and the sternum, progressing in exercise difficulty, first with eyes open and then closed. The subjects were measured before and after proprioception training, for active joint position sense, level of pain, using a visual analog scale (VAS), and knee function, assessed by the international knee documentation committee (IKDC).

Both groups progressed, with significant gains from baseline to follow-up in Absolute Error (AE), Variable Error (VE), VAS for pain, and IKDC ($p<0.05$). The improvements of AE and VE in the HT group were significantly greater than in the CT group ($p<0.001$ for both comparisons), with no difference between groups for the other measures.

Conclusion: This study of patients with recent anterior cruciate ligament reconstruction found that aquatic proprioceptive retraining could improve proprioceptive efficiency.

Hajouj, E., et al. Effects of Innovative Aquatic Proprioceptive Training on Knee Proprioception in Athletes with Anterior Cruciate Ligament Reconstruction: A Randomized, Controlled Trial. **Arch Bone Joint Surg.** 2021, September; 9(5): 519-526.

TUMEFACTIVE MULTIPLE SCLEROSIS PROGNOSIS

Multiple sclerosis (MS) presenting with tumefactive demyelination lesions pose a clinical challenge. Only limited retrospective studies regarding biopsy confirmed MS have described long-term outcomes. This study of patients with central nervous system demyelination, consistent with MS, reviewed the long-term outcomes of these patients, with comparisons to patients with other MS pathology.

All subjects had undergone a prior diagnostic brain biopsy demonstrating MS pathology and had at least one early, active demyelinating lesion. The medical records were reviewed for the medical course over an average of 11 years. Disability was measured using the Expanded Disability Status Scales (EDSS).

Data were completed for 75 patients with confirmed CNS demyelination, with an average age at first attack of 41 years. Tumefactive presentation was identified in 62 of 75 at the initial scan, with biopsy lesion fulfilling criteria of greater than or equal to 2 cm in size, with associated, significant edema. Cognitive outcomes of these patients were below age-normed standards in psychomotor, attention, working memory, and executive function domains. Total lesion volume and index lesion-related severity correlated with EDSS scores and cognitive performance. Sixty-three presented as having relapsing-remitting MS.

Conclusion: This study of tumefactive multiple sclerosis found that the cognitive and disability scores correlated with the central nervous system lesion volume, and that the clinical course was comparable to typical MS in the study.

Kalinowska-Lyszczarz, A., et al. Long -Term Clinical, MRI, and Cognitive Follow-Up in a Large Cohort of Pathologically Confirmed, Predominantly Tumefactive Multiple Sclerosis. **Mult Scler.** 2021 Jul 2:13524585211024162. doi: 10.1177/13524585211024162.

N-3 AND N-6 FATTY ACIDS AND MIGRAINE

The n-3 and n-6 fatty acids serve as precursors for several families of bioactive lipid mediators that regulate pain. Oxylipin derivatives of n-6 linoleic acid have been shown to sensitize trigeminal nerve endings and evoke pain responses. In contrast, several oxylipins derived from n-3 eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have potent antinociceptive (pain reducing) properties. This study investigated the effects of diets with differing amounts of these oxylipins.

Subjects were adults with migraine headaches, randomized to one of three diets. The H3 diet was designed to increase EPA+DHA to 1.5 g/day while maintaining average U.S. intake of linoleic acid (7.2% of energy). The H3-L6 diet was designed to increase EPA+DHA to 1.5 g/day and concurrently decrease n-6 linoleic acid to ≤1.8% of energy. The control diet maintained average

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U.S. intakes of EPA+DHA (<150 mg/day) and linoleic acid (7.2% of energy). The primary clinical endpoint was the Six-Item Headache Impact Test (HIT-6).

Data were collected for 182 participants, including 61 assigned to the H3-L6 group, 61 to the H3 group and 60 to the control group. Compared with the control group, fewer headache hours per day were noted for those in the H3 group ($p \leq 0.001$) and H3-L6 groups ($p \leq 0.001$). As also compared to the control group, both groups noted a reduction in moderate to severe headaches per day ($p \leq 0.001$ for both comparisons). The H3-L6 diet decreased headache days per month more than the H3 diet, suggesting additional benefit from lowering dietary linoleic acid ($p=0.001$).

Conclusion: This study of patients with chronic migraine headaches found that headache frequency could be reduced by diets with increased n-3 eicosapentaenoic acid and docosahexaenoic acid to 1.5 g/day, and decreased n-6 linoleic acid to ≤1.8% of energy.

Ramsden, C., et al. Dietary Alteration of N-3 and N-6 Fatty Acids for Headache Reduction in Adults with Migraine: Randomized, Controlled Trial. **BMJ.** 2021; 3 C4: n1448.

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