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COMPLICATIONS OF CAST REMOVING OSCILLATING SAWS

The power oscillating saw, introduced by Stryker in 1943 was designed to cut the hard cast material but not the soft material underneath. This study reviewed the injuries that occur during cast removal with this device.

The subjects were 208 patients, five years of age or older, presenting for cast removal. The patients were divided into two groups, with both groups using the striker oscillating saw. The casts were removed in Group 1 using conventional protection methods and in Group 2 using tongs shaped with an externally guided steel plate aid for skin protection. Injuries and the severity of injuries were recorded for each group.

In Group 1, the skin laceration rate was 0.9%, and the rates of burn sensations and burn findings (first and second-degree burns) were 21.7% and 2.8%, respectively. Moderate anxiety was reported by 57% of Group one and six percent of Group 2. Participants in Group 2 experienced no skin lacerations, severe burns or severe anxiety.

Conclusion: This study introduced a novel means of cast removal which eliminated complications such as skin laceration (resulting in bleeding), visible burn, and severe anxiety.

Sevencan, A., et al. Current Complications of Cast Removal with Oscillating Saws and a Novel Method for Reducing Such Complications. A Comparative Clinical Study. **J Bone Joint Surg Am**. 2022, September 28; 00: 1-7 DOI:10.2106/JBJS.21.01556.

SINGLE DOSE PSILOCYBIN FOR MAJOR DEPRESSION

Preliminary studies have suggested that psilocybin may have antidepressant efficacy for patients with major depressive disorder. This trial was designed to identify an acceptable and efficacious dose of psilocybin for patients with treatment-resistant major depressive episodes.

This phase two double-blind parallel-group randomized clinical trial included adults, 18 years of age or older with a diagnosis of treatment-resistant major depressive disorder. The patients were randomly assigned in a 1:1:1 ratio to receive a single dose of psilocybin at 25 -mg, 10 -mg, or 1 -mg (control). After the treatment, the subjects were followed for 12 weeks. The primary endpoint was the change from baseline to week three in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score.

Subjects included 233 patients of whom 24 had withdrawn by week 12. By week three the mean change in the MADRS total score was −12.0 points in the 25-mg group, −7.9 in the 10-mg group, and −5.4 in the 1-mg group. The difference in improvement between the control group and the 25 -mg group reached statistical significance ($p<0.001$), but the 10-mg group did not ($p=0.18$). The incidence of sustained response at week twelve was 20% in the 25 -mg group, 5% in the 10 -mg group, and 10% in the 1 -mg group.

Conclusion: This study of patients with treatment-resistant depression found that a single dose of 25 -mg psilocybin could improve depression scores with 20% realizing a sustained relief at 12 weeks.

Goodwin, G., et al. Single Dose Psilocybin for a Treatment Resistant Episode of Major Depression. **N Engl J Med**. 2022, November 3; 387(18): 1629-1724.

TERIPARATIDE TREATMENT IN SEVERE OSTEOPOROSIS

Teriparatide was approved by the European Medicines Agency in 2003 as the first anabolic agent for established osteoporosis. This study reviewed the long-term outcomes of patients treated with Teriparatide for at least 18 months.

This study is a follow-up of a randomized, double-blind, placebo-controlled, prospective study of growth hormone, administered to postmenopausal women with osteoporosis. Women with established osteoporosis and at least one vertebral compression fracture were included consecutively from 2004 until 2013. Participants in the treatment arm received 20 micrograms daily of teriparatide for up to two years. Bone mineral density was measured at baseline, at months 18 and 36, and then at 10 years. Two hundred thirty-three women of similar age from a random population sample served as controls.

Forty women with a mean age of 69 years began the trial. Of these, 14 died and 20 completed the 10-year follow-up. Fractures declined from 100% to 35%, rates comparable to the population sample. Thirteen of the 20 women who completed the 10 years did not experience any further fractures. Total well-being, as measured by the EQ5D-VAS, was lower in patients with osteoporosis before treatment compared to population controls and did not significantly improve during the 10-year follow-up.

Conclusion: This study of postmenopausal women with osteoporosis fractures found that teriparatide could reduce the fracture prevalence to levels similar to those of the general population.

Kontogeorgos, G., et al., Teriparatide Treatment in Severe Osteoporosis-A Controlled, 10-Year Follow-Up Study. **BMC Musc Disord**. 2022; 23: 1011.

TRAUMATIC BRAIN INJURY AND SUBSEQUENT CARDIOVASCULAR DISEASE

Previous studies have demonstrated associations between traumatic brain injury (TBI) and both hemorrhagic and ischemic stroke. Given the high prevalence of TBI in post-911 military veterans, this study explored the association between TBI

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and subsequent cardiovascular disease.

The subjects were United States military veterans who had served in the military after 9/11/01. Data were obtained from the U.S. Department of Veterans Affairs (VA) and the U.S. Department of Defense (DoD) Identity Repository (VADIR), the VA Corporate Data Warehouse (CDW), the DoD and VA Infrastructure for Clinical Intelligence (DaVINCI), the Theater Data Management Store (TMDS), the DoD Trauma Registry (DoDTR), and the National Death Index (NDI). Those participants with a diagnosis of TBI were compared to a matched control group without a history of TBI. The subjects were followed until December 31, 2018. The primary endpoint was cardiovascular disease (CVD) defined as a composite of coronary artery disease, stroke, peripheral artery disease and cardiovascular death.

Data were gathered for 301,169 veterans with a TBI and 1,258,759 without a TBI. Multivariable analysis revealed that, as compared to those without a history of TBI, CVD was more prevalent in those with a mild TBI ($p<0.001$), moderate to severe TBI ($p<0.001$), and penetrating TBI ($p<0.001$). In addition, compared to controls, the risk was greater among those with a TBI for cardiac death stroke, PAD, and CAD.

Conclusion: This cohort study of military veterans found that traumatic brain injury was independently associated with cardiovascular disease.

Stewart, I., et al. Association between Traumatic Brain Injury and Subsequent Cardiovascular Disease among Post-911 Era Veterans. **JAMA Neuro**. 2022 Nov 1;79 (11):1122-1129.

DAILY LOW DOSE ASPIRIN AND FALLS IN HEALTHY ELDERLY

Globally, more than 1.6 million hip fractures occur annually. As research has demonstrated that aspirin may reduce bone fragility and falls, this study was designed to determine whether daily low-dose aspirin is associated with decreased incidence of any fracture in elderly, healthy women, and men.

The ASPREE-FRACTURE sub-study was a double-blind, randomized, placebo-controlled trial of healthy individuals, 70 years of age or older, conducted in Australia within the Aspirin in Reducing Events in the Elderly (ASPREE) clinical trial. The subjects were randomized to receive either daily 100 milligrams of aspirin or a placebo. The primary outcome of this study was the occurrence of any fracture after randomization. The secondary outcome was a serious fall, defined as requiring a fall-related hospital presentation.

Participants included 8,322 in the aspirin group and 8,381 in the placebo group. At a median follow-up of 4.6 years, serious falls were reported in 9.0% of the aspirin group and 8.2% of the placebo group ($p=0.01$). The cumulative risk of fractures was not significantly different between the two groups.

Conclusion: This study of healthy individuals 70 years of age or older found that low-dose aspirin failed to reduce the risk of fractures while increasing the risk of serious falls.

Barker, A., et al. Daily Low Dose Aspirin and Risk of Serious Falls and Fractures in Healthy Older People. A Sub-Study of the ASPREE Randomized Clinical Trial. **JAMA Intern Med.** 2022 Dec 1;182 (12):1289-1297.

LYME NEUROBORRELIOSIS WITH ANTIBODIES IN CEREBRAL SPINAL FLUID BUT NOT IN SERUM

Lyme neuroborreliosis (LNB) is a tick-borne infection caused by the spirochete *Borrelia burgdorferi* sensu lato. To diagnose LNB, cerebrospinal fluid (CSF) is tested for pleocytosis and intrathecal antibody production. However, some guidelines recommend a lumbar puncture only in case of positive *Borrelia* serology or a strong clinical suspicion of LNB. This study was designed to better understand the frequency of negative serology in cases of suspected LNB.

This retrospective study was performed among patients diagnosed with LNB between January of 2007 and December of 2020. Records were reviewed for patients with pleocytosis and symptoms suggestive of LNB. Pleocytosis was defined as a leukocyte cell count in CSF >15/3 per µL. Data were reviewed from the charts of 127 patients diagnosed with LNB. The clinical manifestations included cranial nerve palsy, radiculitis, or meningitis.

In 67 patients, *Borrelia* antibodies were present in both serum and CSF. In 28 patients, there was intrathecal antibody production, while serum antibodies were absent. Of the patients with positive serology, 77% had antibodies in CSF versus 83% of

patients with negative serology (p=0.435). Of patients with positive serology, 61% had intrathecal antibody production versus 78% of patients with negative serology.

Conclusion: This study of patients with Lyme neuroborreliosis found that 28 had antibody production in the cerebrospinal fluid with no antibodies found in the serum. The authors suggest a need to lower the threshold for a lumbar puncture in patients with suspected Lyme disease.

Zomer, T., et al. Lyme Neuroborreliosis with Antibodies in Cerebrospinal Fluid but not in Serum. **Eur J Neurol** . 2022 Nov 12. doi: 10.1111/ene.15631.

TRANSCUTANEOUS AURICULAR VAGUS NERVE STIMULATION AND MILD COGNITIVE IMPAIRMENT

Vagus nerve stimulation (VNS) has been shown to be a promising treatment for the improvement of cognitive function in patients with epilepsy. As the vagus nerve distribution includes an area on the surface of the auricular concha, this study assessed the efficacy of auricular VNS (aVNS) to address cognitive function in patients with mild cognitive impairment (MCI).

This double-blind placebo-controlled trial recruited patients 35 to 75 years of age with a diagnosis of MCI. The participants were randomized to receive aVNS or sham stimulation. In the aVNS group, a pair of auricular acupoints were stimulated, including heart (concha, CO15) and kidney (CO10), in the distribution of the vagus nerve. Those in the sham group were stimulated at a pair of auricular acupoints out of the distribution of the vagus nerve; the elbow (scaphoid fossa, SF3) and shoulder (SF4,5). All participants underwent two 30-minute sessions five days per week for 24 weeks. The primary outcome measure was the Montreal Cognitive Assessment Basic (MOCA-B).

Before intervention, there was no significant difference between groups in the scores on the MOCA-B. Compared to the baseline, scores on the MOCA-B improved in the aVNS group (p<0.001) but not in the sham group (p=0.338). The improvement in MOCA-B scores was greater in the aVNS than in the sham group (p<0.001). Among the secondary outcomes, greater improvement from baseline to follow-up was found in the aVNS group for the Auditory Verbal Learning Test-Huashan Version (p=0.047) and the shape Trails Test B (p<0.001), but not for the Animal Fluency Test, Boston Naming Test, Pittsburgh Sleep Quality Index, Rapid Eye Movement Sleep Behavior Disorder Screening Questionnaire, Epworth Sleepiness Scale, or Functional Activities Questionnaire.

Conclusion: This study of patients with mild cognitive impairment found that 24 weeks of vagus nerve stimulation at the ear could improve MOCA-B cognitive scores.

Wang, L., et al. The Efficacy and Safety of Transcutaneous Auricular Vagus Nerve Stimulation in Patients with Mild Cognitive Impairment: A Double-Blinded, Randomized Clinical Trial. **Brain Stim**. 2022, November and December; 15(6): 1404-1414.

TRANSCUTANEOUS ARTICULAR VAGUS NERVE STIMULATION AND SALIVARY ALPHA-AMYLASE

Non-invasive transcutaneous auricular vagus nerve stimulation (taVNS) has been explored as a brain stimulation tool for the treatment of epilepsy, depression, and chronic pain. One mechanism for the taVNS effect involves the activation of the locus coeruleus- noradrenaline (LC-NA) system. This study assessed the effect of taVNS on salivary alpha-amylase (sAA), an indirect marker of LC-NA.

Data were obtained from ongoing and previous taVNS studies which collected sAA data, including three unpublished studies. From these, sAA levels were available for 371 healthy participants. All studies used taVNS stimulation conducted with the stimulator electrodes placed in the left cymba conchae, an area exclusively innervated by the auricular branch of the vagus nerve. The sham stimulator was placed in the center of the left earlobe, an area free of vagal innervation. Levels of sAA in the saliva were collected before and after the simulation.

Using a linear mixed model analysis, sAA levels after stimulation were increased significantly more in the taVNS group than in the sham group (p=0.001). The analysis was underpowered and did not demonstrate significant differences between the groups.

Conclusion: This study of vagus nerve stimulation at the ear found that this stimulation increases the release of salivary alpha-amylase, substantiating that this stimulation triggers the release of noradrenaline.

Giraudier, M., et al. Evidence for a Modulating Effect of Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) on Salivary Alpha Amylase as Indirect Noradrenergic Marker: A Pooled Mega-Analysis. **Brain Stimul**. 2022 Sep 30;15(6):1378-1388.

HAND GRIP STRENGTH TO DIAGNOSE SARCOPENIA

In defining sarcopenia, both the European Working Group on Sarcopenia in Older People (EWGSOP2) and the Asian Working Group for Sarcopenia (AWGS2019) recommend using either hand grip strength (HGS) or the chair stand test (CST) as a first step. This study was designed to determine the agreement between the prevalence of sarcopenia using either HGS or CST and the efficacy of proposed strength cutoffs in predicting health outcomes.

Data were obtained from a longitudinal cohort of geriatric rehabilitation inpatients admitted to the department of aged care at the Royal Melbourne Hospital in Victoria, Australia. Within 48 hours of admission, the physical, cognitive, and physiologic health of the patients was assessed using the Comprehensive Geriatric Assessment (CGA). The subjects were followed after discharge, with outcomes including readmission and mortality. Grip strength was measured six times, with the maximum value recorded. Physical performance was assessed with the Short Physical Performance Battery (SPPB), which includes a standing balance test, a four-meter walk test for gait speed, and the CST. The EWGSOP2 and AWGS2019 definitions and cut-offs were used for the sarcopenia diagnosis.

Data were completed for 1,052 patients with a median age of 83.1 years. An adjusted analysis revealed that HGS was associated with three-month institutionalization (p=0.009) as well as three- (p=0.022) and 12-month (p=0.008) mortality. No significant association was found with CST. Neither of the tests was associated with hospital readmission within three months.

Conclusion: This Australian study of elderly patients admitted to an inpatient rehabilitation facility found hand grip strength to be useful in predicting three- and 12-month

mortality, as well as three-month institutionalization.

Verstraeten, L., et al. Hand Grip Strength Rather Than Chair Stand Test Should be Used to Diagnose Sarcopenia in Geriatric Rehabilitation Inpatients: Restoring Health of Acutely Unwell adults (RESORT). **Age Aging.** 2022; 51(11): 1-9. doi: 10.1093/ageing/afac242. PMID: 36413590.

DENOSUMAB AND ORAL BISPHOSPHONATES TO TREAT GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Glucocorticoid use has been a critical cause of secondary and drug-induced osteoporosis. Bisphosphonates are the most commonly used drugs for the treatment of local glucocorticoid-induced osteoporosis. For patients unable to use bisphosphonates, denosumab has been found to be effective. However, the relative efficacy of these two is not clear. Therefore, this literature review and meta-analysis was designed to clarify the advantages and disadvantages of these two medications.

A literature search was completed, with four randomized, controlled trials chosen for inclusion. From these, data of 714 patients treated with denosumab and 357 treated with bisphosphonates were included in the analysis. Percentage changes in lumbar spine bone mineral density (BMD) at six and 12 months were presented in three and four of the studies, respectively. Denosumab was superior in increasing lumbar spine BMD at six and 12 months ($p<0.001$ for both comparisons). In the pooled analysis of femoral neck BMD, no significant difference was seen over time between the two treatments performed at six months or 12 months. For the hip, the percent changes in BMD did not differ at six months but were superior in the denosumab group in the ultra-distal radius at 12 months ($p=0.0003$).

Conclusion: This study of women with glucocorticoid-induced osteoporosis found that, compared with bisphosphonates, denosumab was superior for improving lumbar spine bone mineral density, with no significant differences in the total hip and femoral neck.

Jiang., et al. Comparison of Denosumab and Oral Bisphosphonates for the Treatment of Glucocorticoid-Induced Osteoporosis: A Systematic Review and Meta-Analysis. **BMC Musculoskel Dis**. 2022; 23: 1027.

NAOXINTONG CAPSULE FOR THE SECONDARY PREVENTION OF ISCHEMIC STROKE

In a systematic analysis of the global burden of disease study in 2019, stroke was identified as the leading cause of years of loss of life in China. In Chinese medicine, an ischemic stroke (IS) is thought to be the result of blood stasis. Naoxintong Capsule is widely used in China for patients with an IS as well as coronary artery disease. The capsule is a combination of multiple natural agents. Previous studies have suggested that this medication may regulate cytokines, vascular growth factors, angiogenesis, and lipid profiles. This multicenter, randomized, controlled trial evaluated the effect of Naoxintong Capsule on the occurrence of ischemic stroke.

Subjects included 2,200 patients ages 18 to 80 years of age diagnosed with acute IS. The patients were randomized to receive either Naoxintong Capsule 1.2 grams twice per day or a placebo in addition to standard care (2014 Chinese guidelines recommend aspirin (75–150 mg/d) monotherapy and (or) clopidogrel (75 mg/d) monotherapy in patients with noncardioembolic IS). The primary outcome was recurrent IS.

At the two-year follow-up, IS was found in 6.5% of the treatment group and 9.5% of the placebo group ($p=0.008$). Myocardial infarction was identified in 0.3% of the treatment group and 0.5% in the control group ($p=0.5$). Among those with an IS under 65 years of age, recurrent stroke occurred in 5.1% of the treatment group and 11% of the placebo group($p=0.0011$). There were no significant differences between the two groups in the occurrence of severe hemorrhage, cerebral hemorrhage, or subarachnoid hemorrhage.

Conclusion: This study of patients with ischemic stroke found that the traditional Chinese medicine, Naoxintong Capsule, significantly reduced the risk of recurrent ischemic stroke.

Yu, X.F., et al. Naoxintong Capsule for Secondary Prevention of Ischemic Stroke: A Multi-Center, Randomized, and Placebo-Controlled Trial. **Chin J Integr Med**. 2022, December; 28(12): 1063-1071.

COMPARISON OF DIRECT ORAL ANTICOAGULANTS FOR ATRIAL FIBRILLATION

For patients with atrial fibrillation (AF), there is no clear guidance on how to choose among the four available direct oral anticoagulants (DOACs). This study compared the efficacy and safety outcomes of patients with AF who were prescribed apixaban, dabigatran, edoxaban, or rivaroxaban.

Data were obtained from anonymized patient records from five electronic health databases in the distributed data network of the Observational Health Data Science and Informatics (OHDSI) program. Data were reviewed for head-to-head target trials for each pairwise comparison of the four DOACs. Eligible patients were at least 18 years with a diagnosis of AF and had never used a DOAC. The outcomes of interest were a composite of ischemic stroke and systemic embolism, intracranial hemorrhage (ICH), gastrointestinal bleeding, and all-cause mortality.

Data were available for 527,226 new users, including those who were prescribed apixaban (n=281,320), dabigatran (n=61,008), edoxaban (n=12,722), or rivaroxaban (n=172,176). After propensity score stratification, no statistically significant differences were noted among DOACs for ischemic stroke, systemic embolism, ICH, or all-cause mortality. The risk for a GI bleed was lower for apixaban as compared to dabigatran (Hazard Ratio (HR) 0.81), rivaroxaban (HR 0.72), or edoxaban (HR 0.77).

Conclusion: This study of patients with atrial fibrillation, using DOACs therapy, found that stroke, systemic embolism, intracranial hemorrhage, and all-cause mortality were similar among DOACs, while the risk of gastrointestinal bleeding was lowest among those who received apixaban.

Lau, W., et al. Comparative Effectiveness and Safety between Apixaban, Dabigatran, Edoxaban, and Rivaroxaban among Patients with Atrial Fibrillation: A Multinational, Population-Based, Cohort Study. **Ann Intern Med**. 2022, November; 175 (11): 1515-1525.

APIXABAN VERSUS RIVAROXABAN FOR ATRIAL FIBRILLATION WITH VALVULAR HEART DISEASE

Atrial fibrillation (AF) increases the risk of stroke and death. Of those with AF, 63.5% have concurrent valvular heart disease (VHD). As previous large studies of patients with AF have excluded those with VHD, this study evaluated the risk of ischemic and bleeding events among those with both AF and VHD.

This study compared the efficacy and safety of apixaban with that of rivaroxaban among patients with AF and VHD. Data were obtained from a commercial database of privately insured individuals. Patients with AF and VHD who were using apixaban were compared to those using rivaroxaban. The primary efficacy outcome was a composite of ischemic stroke or systemic embolism. The safety outcome variable was a composite of gastrointestinal (GI) bleeding or intracranial bleeding.

Data were included for 23,712 patients prescribed apixaban and 10,195 prescribed rivaroxaban. In a propensity score-matched sample of patients, the rates of ischemic stroke or systemic embolism per 1,000 person-years of follow-up were 5.2 among those taking apixaban and 9.1 among those taking rivaroxaban (Hazard Ratio (HR) 0.57). Finally, the rates of GI or intracranial bleed per 1,000 person-years of follow-up were 14.3 among those using apixaban and 28.1 among those using rivaroxaban (HR 0.51).

Conclusion: This study of patients with atrial fibrillation and valvular heart disease found that the risk of stroke, ischemic embolism, gastrointestinal bleeding, or intracranial bleeding was lower among subjects prescribed apixaban than among those prescribed rivaroxaban.

Dawwas, G., et al. Apixaban versus Rivaroxaban in Patients with Atrial Fibrillation and Valvular Heart Disease. A Population-Based Study. **Ann Intern Med.** 2022, November; 175(11): 1506-1514.

REPEAT POST-TRAUMATIC CT IN ELDERLY WITH HEAD TRAUMA AND ANTITHROMBOTIC USE

For patients undergoing evaluation for a mild traumatic brain injury (mTBI) who are taking anti-thrombotic (AT) agents and have a normal initial computed tomography (CT) study, there is no clear consensus regarding follow-up imaging. This study evaluated the utility of a repeat CT for older patients with mTBI presenting to the emergency department (ED) with an ongoing antithrombotic prescription.

This retrospective study involved a manual chart review of patients ≥55 years of age presenting to a level I or II trauma center between 2017 and 2019. All had Glasgow Coma Scale (GCS) scores of 14 to 15, a negative initial brain CT and were being evaluated for suspected brain trauma. The exposure of interest was pre-injury AT status. The primary outcome of the study was a delayed intracerebral hemorrhage (dICH), defined as cerebral edema, intra-ventricular hemorrhage, subdural hemorrhage, cerebral contusion, subarachnoid hemorrhage, or epidural hemorrhage, discovered on a repeat CT within 48 hours of the initial scan.

Records from 24 centers were screened, with 2,950 within the eligibility parameters. Among the 949 patients with ongoing AT therapy, 9.5% had a repeat CT scan, of whom 7.5% had sustained a new ICH. In an adjusted analysis, no significant association was found between pre-injury AT status and dICH. Among those patients without a repeat CT, no surgical interventions were performed.

Conclusion: This retrospective study reviewing the outcomes of patients ≥55 years of age, presenting to the ED with head trauma, found that an ongoing prescription of antithrombotic agents did not significantly increase the risk of intracerebral hemorrhage.

Flaherty, S., et al. Findings on Repeat Post-Traumatic Brain Computed Tomography Scans in Older Patients with Minimal Head Trauma and the Impact of Existing Antithrombotic Use. **Ann Emerg Med**. 2022. In Press. doi.org/10.1016/j.annemergmed.2022.08.006.

FRONTOTEMPORAL LOBAR DEGENERATION AND NEUROFILAMENT LIGHT CHAIN

While genetics play a large part in the risk of dementia, up to a dozen lifestyle factors are implicated in brain health across the lifespan. Frontotemporal lobar degeneration (FTLD) is among the more common causes of dementia in adults ≤65 years of age. This study evaluated the association between physical activity and a molecular correlate of neurodegeneration, plasma neurofilament light chain (NFI).

This cohort study included individuals with pathogenic variants in one of three common genes associated with FTLD (GRN, C9orf72, or MAPT). All participants completed a baseline and at least two follow-up annual visits. Evaluations were made of physical activity, with blood drawn to determine NFI concentrations. The clinical severity of the disease was measured by the CDR+NACC FTLD and the Unified Parkinson's Disease Rating Scale (UPDRS).

Greater baseline physical activity was associated with slower NFI trajectories. Among those with average physical activity, NFI was estimated to increase 45.8% / 4 years. Compared to those with low physical activity, those with high activity had a 30.3% slower NFI progression over four years. Pairwise comparisons found that the weakest association between physical activity and NFI trajectories was found in those with the GRN variant. Stratifying by genotype, high physical activity was associated with a 21.0% (C9orf72*)* and 18.4% (MAPT*)* slowing of NFl over four years. Higher participation in household work, yard work, and sports were most strongly associated with NFI trajectories, with 12.9%-19.6% slower trajectories.

Conclusion: This study of patients with frontotemporal lobar degeneration found that those with higher reported physical activity had a slower progression of neurofilament light, a marker of axonal degeneration.

Casaletto, K., et al. Association of Physical Activity With Neurofilament Light Chain Trajectories in Autosomal Dominant Frontotemporal Lobar Degeneration Variant Carriers. **JAMA Neurol**. 2022. doi:10.1001/jamaneurol.2022.4178.

WEIGHTED BLANKETS AND MELATONIN

Weighted blankets have emerged as a potential nonpharmacological intervention to reduce insomnia and anxiety. This study was designed to investigate whether a weighted blanket at bedtime would result in higher salivary concentrations of melatonin and oxytocin.

Twenty-six normal-weight young non-smoking men and women were recruited. The subjects were also asked about sleep and dietary habits

and were scored on the Morningness-Eveningness questionnaire. In a crossover design, patients were randomly assigned to first use the weighted blanket or the unweighted blanket. The blankets were placed to cover the extremities come abdomen and chest in a supine position one hour before and during eight hours of sleep opportunity. The blankets were weighted to 12.2% of the participants' body weight (weighted) or 2.4% of the participants' body weight (Control). Saliva was collected every 20 minutes between 10 and 11:00 PM with subjective sleepiness assessed every 20 minutes using a Karolinska Sleepiness Scale (KSS).

Salivary melatonin concentrations rose between 10:00 PM and 11:00 PM with the average increase greater in the weighted blanket condition (p=0.011). No other significant differences were found between the blanket conditions, including serum oxytocin, subjective sleepiness, and total sleep duration.

Conclusion: This study comparing waited and unweighted blanket used during sleep found an increase in melatonin with the weighted blankets though no difference in subjective or objective measures of sleep.

Meth, E., et al. A Weighted Blanket Increases Pre-Sleep Salivary Concentrations of Melatonin in Young, Healthy Adults. **J Sleep Research** 2022, Oct 3. doi: 10.1111/ jsr.13743. Epub Ahead of Print.

SECOND LINE GLUCOSE LOWERING DRUGS

Type 2 diabetes is a chronic health condition that affects 9.3% of people worldwide. Metformin is the preferred glucose-lowering drug due to its efficacy, tolerability and low cost. The GRADE (Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study) trial is a recently completed, but still unpublished, pragmatic, randomized, parallel-arm clinical trial designed to address this knowledge gap by comparing four second-line glucose-lowering drugs among adults with moderately uncontrolled type 2 diabetes who are in receipt of metformin monotherapy. The drugs represent four classes: glimepiride (sulfonylurea), sitagliptin (dipeptidyl-peptidase 4 inhibitor), liraglutide (glucagon-like peptide-1 receptor agonist), and insulin glargine (basal analog insulin).

Subjects were adults with type 2 diabetes glycated hemoglobin A_{1c} (HbA_{1c}) levels of 6.8 to 8.5% while using metformin monotherapy, who then added a second-line drug. Using claims data from the OptumLabs Data Warehouse (OLDW), a deidentified national dataset of privately insured and Medicare Advantage beneficiaries, patients were identified who added glimepiride, sitagliptin, liraglutide, or insulin glargine. The primary outcome was time to primary metabolic failure defined as days to HbA_{1c} ≥7.0% while treated with the assigned drug.

The median time to primary metabolic failure was 442 days in the glimepiride arm, 764 days in the liraglutide arm, and 427 days in the sitagliptin arm. Liraglutide was associated with the lowest risk of secondary metabolic failure, and the lowest cumulative incidence of secondary metabolic failure.

Conclusion: This study of patients with diabetes treated with metformin found that for secondary treatment, liraglutide was more effective at maintaining glycemic control than either glimepiride or sitagliptin.

Deng, Y., et al. Emulating the GRADE Trial Using Real-World Data: Retrospective Comparative Effectiveness Study. **BMJ.** 2022; 379:

MINOCYCLINE AFTER TRAUMATIC BRAIN INJURY

After a traumatic brain injury (TBI), neuroprotective agents have shown promise when administered before or very early post-injury. Minocycline is a broad-spectrum tetracycline antibiotic that has been studied as a neuroprotective agent. The mechanism for this process is thought to be the suppression of microglial activation after TBI. This animal study explored different regiments of minocycline dosing in order to better understand the long-term efficacy of minocycline

The subjects were eight-week-old mice, undergoing a craniectomy followed by a sham or controlled cortical impact (CCI) designed to produce a moderate level of injury. One day after surgery, those undergoing CCI were subjected to 60 minutes of hypoxemia (8% O_2, 4% CO_2). The animals were randomized to receive an intraperitoneal placebo or minocycline, at 45 mg/kg, 90 mg/ kg, or 180 mg/kg. For three of the groups, the respective doses were repeated on postinjury days two and three. For the fourth minocycline group, after receiving an initial dose of minocycline 90 mg/kg two hours prior to hypoxemia, the mice received an additional five doses of minocycline 45 mg/kg every 12 hours. Efficacy was assessed by quantifying the neurons in the CA3 region of the hippocampus.

Minocycline 45mg/kg once per day showed no benefit in preserving CA3 neurons, while both dosing regimens with an initial dose of 90 mg/kg demonstrated a similar reduction in neuronal loss. The hippocampus, flow cytometry studies found a reduction in the total number of microglia and a reduction in the number of microglia that expressed major histocompatibility complex II. Reviewing the neuroinflammatory response, compared to the sham group, the minocycline group demonstrated a reduced infiltration of peripheral lymphocytes ($CD3^+$) and monocytes ($Ly6C^+$). Behavior tests demonstrated an improvement in the contextual-fear response in the minocycline group compared to the sham group ($p < 0.00001$).

Conclusion: This animal study found that a short course of minocycline resulted in a reduction of acute microglial activation, monocyte infiltration and hippocampal neuronal loss at one-week post-injury.

Celorrio, M., et al. Acute Minocycline Administration Reduces Brain Injury and Improves Long-Term Functional Outcomes after Delayed Hypoxemia following Traumatic Brain Injury. **Acta Neuropathol Comm.** 10, 10 (2022). https://doi.org/10.1186/s40478-022-01310-1.

TRIGLYCERIDE LOWERING WITH PEMAFIBRATE TO REDUCE CARDIOVASCULAR RISK

Elevated triglyceride levels are associated with an increased risk of cardiovascular events. This study assessed the effects of pemafibrate, a selective peroxisome proliferator-activated receptor α (PPARα) modulator, on serum triglyceride (TG) levels and its effect on subsequent cardiovascular events.

The Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes (PROMINENT) trial is a double-blind, placebo-controlled trial of patients with type 2 diabetes, TG levels of 200-500mg/dL, and HDL levels of ≤40 mg/dL. The subjects were randomized to receive either pemafibrate (0.2-mg tablets twice daily) or a matching placebo, and were contacted at two, four, six, eight, and 12 months, and then every four months thereafter. The primary endpoint was the first occurrence of a major cardiovascular event, with this modified three years after the study

onset to include any coronary revascularization.

Data were complete for 10,497 patients with a median age of 64 years and a mean follow-up of 3.4 years. At four months, the median changes in fasting TG levels from baseline were -31% in the pemafibrate group and -6.9% in the placebo group. Similar, relative reductions were noted on measures of very-low-density lipoprotein cholesterol (−25.8%). The primary endpoint event occurred in 572 patients in the treatment group and in 560 in the placebo group (p=0.67). The effects were neutral for all composite, secondary cardiovascular endpoints, as well as for the hazard ratio for death from any cause.

Conclusion: This large study of patients with type 2 diabetes and mild -to-moderate hypertriglyceridemia found that, although pemafibrate, a selective peroxisome proliferator-activated receptor α (PPARα) modulator, significantly lowered triglyceride levels, there was no beneficial effect on any cardiovascular endpoint.

Pradhan, A., et al. Triglyceride Lowering with Pemafibrate to Reduce Cardiovascular Risk. **N Engl J Med.** 2022. November 24; 387(21): 1923-1934.

SLEEP RESTRICTION AND RESISTANCE EXERCISE IN FEMALES

Recent data have demonstrated that up to 70% of athletes report difficulties with sleep. This study investigated the effect of sleep restriction on resistance exercise performance and perceived fatigue in resistance-trained females.

Subjects were 10 resistance-trained females ages 18-35 years. During the study, subjects continued their resistance training regimen. All participants were tested for baseline 3 repetition maximum (3 Rep Max) strength measurements for back squat, bench press, seated row, trap bar deadlift, leg press, and lat pull-down exercises. The participants were randomly allocated to the sleep restriction (SR) or normal sleep (NS) group. The SR trial consisted of a nine-night stay within the sleep laboratory, whereby participants spent 5-h time-in-bed (0100-0600 h) each night. The NS group were required to sleep normally at home, with a bedtime between 2200 and 0000 h and wake time before 0800 h. After a 12-week washout, the roles were reversed.

During the trial, the mean sleep duration was 4.7 hours in the SR group and 7.3 hours in the NS group ($p<0.0005$). The SR group experienced reduced session volume load relative to 1RM ($p = 0.03$) and total repetitions performed ($p= 0.03$). The SR group experienced significantly decreased average mean concentration velocity (MCV) for all sets of back squats (all $p< 0.02$). Furthermore, MCV was slower in the SR group on the second repetition of set one ($p = 0.04$) and the final repetition of set four ($p< 0.01$), demonstrating greater fatigue both before and after, respectively. SR increased salivary cortisol area under the curve (by 42%), total training distress (by 84%), and session perceived exertion (by 11%).

Conclusion: This study of 10 resistance-trained females found that sustained sleep restriction compromised both resistance exercise quantity (volume load) and quality (movement velocity at a given load), as well as perceived training distress.

Knowles, O., et al. Sustained Sleep Restriction Reduces Resistance Exercise Quality and Quantity in Females. **Med Sci Sport Exerc.** 2022, December; 54(12): 2167-2177.

EXERCISE AND ANTIDEPRESSANTS FOR NON-SEVERE DEPRESSION

Depression is a leading cause of disability worldwide, estimated to affect over 320 million people. Previous studies have shown that the effectiveness of antidepressant medications is related to the magnitude of depressive symptoms. Therefore, the benefits of antidepressants in patients with non-severe depression are less robust than those in patients with severe depression. This literature review was designed to better understand the effect of exercise and of antidepressants in patients with non-severe depression.

Databases were reviewed for randomized controlled trials investigating the effect of exercise or antidepressants in adults with non-severe depression. The primary outcome was symptom severity defined as the score on a depression scale at the study completion.

From the 21 studies selected, 2,551 participants were included in 25 pairwise comparisons. These included antidepressants versus controls, exercise versus controls, combined treatments versus antidepressants, and combined treatments versus exercise. At the end of the interventions, compared with controls, exercise, antidepressants, and combined treatments were superior in reducing depressive symptoms. Exercise had a similar benefit to that of antidepressants. The effect of combined treatments was similar to the effect of exercise or antidepressants.

Conclusion: This literature review and network meta-analysis found that, for patients with non-severe depression, exercise, antidepressants, and the combination of these were all equal in efficacy and superior to controls.

Recchia, F., et al. Comparative Effectiveness of Exercise, Antidepressants and Their Combination in Treating Non-Severe Depression: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. **Br J Sports Med.** 2022; 56(23):1375–1380.

ELECTIVE DEGENERATIVE LUMBAR SPINE SURGERY IN THE FRAIL AND SARCOPENIC

With the global aging of the population, degenerative spine disease is becoming increasingly prevalent. When reviewing surgical options for the elderly, frailty is one of the factors that should be considered to optimize outcomes. Frailty is defined as an age-related decline in physiologic reserve which may result in a decreased ability to respond to provoked stress, such as surgery. This study investigated the effect of frailty and sarcopenia on patient-reported outcomes (PRO) following elective lumbar spine surgery in a group of elderly patients.

Subjects were patients ≥70 years of age who underwent elective lumbar spine surgery for degenerative spine disease between 2010 and 2019. Frailty was calculated using the mFI-5 which includes diabetes mellitus, hypertension, congestive heart failure, chronic obstructive pulmonary disease, and dependent functional status. Sarcopenia was defined as the total loss of psoas muscle area, calculated using preoperative lumbar spine magnetic resonance imaging. The primary outcome measure was PRO, evaluated using the Oswestry Disability Index (ODI). Secondary outcomes included the Numeric Rating Scale (NRS) of back pain (NRS-BP), NRS leg pain (NRS-LP), and quality of life, using the EuroQual -5D and the North American Spine Society (NASS) satisfaction

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questionnaire.

Data from 448 patients were included in the final analysis. Compared with the baseline, significant improvements were noted at 12 months in ODS scores ($p<0.001$). Significant improvements were also noted in EuroQual-5D scores as well as NRS-LP, and LRS-BP ($p<0.001$ for all). A multivariable linear regression showed that mFI-5 was a significant predictor of 12-month ODI scores ($p<0.001$) with higher mFI-5 scores associated with worse ODI scores. However, sarcopenia was not found to be a significant predictor of ODI.

Conclusion: This study of elderly adults undergoing elective lumbar spine surgery found that frailty, but not sarcopenia, was a significant predictor of the 12-month patient-rated outcome.

Chotai, S., et al. Frailty and Sarcopenia: Impact on Outcomes Following Elective Degenerative Lumbar Spine Surgery. **Spine.** 2022;47(20):1410-1417. doi:10.1097/BRS.0000000000004384.

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