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FENTANYL AND CARFENTANIL IN DRUG OVERDOSE DEATHS: 2020 TO 2024

In 2013, illegally manufactured fentanyl (IMFs) and fentanyl analogs entered the United States' drug supply. Carfentanil, a fentanyl analog 100 times more potent than fentanyl, is noteworthy among these. This study was designed to describe recent trends in detected IMFs and carfentanil among overdose deaths in the United States.

Data for this report included unintentional overdose deaths obtained from death certificates, coroner and medical examiner reports, and postmortem toxicology reports, entered into the CDC's State Unintentional Drug Overdose Reporting System (SUDORS) from January of 2021 to June of 2024. The number of overdose deaths associated with carfentanil was also tabulated.

From January of 2021 to December of 2023, 251,089 unintentional and undetermined intent drug overdose deaths occurred, including 188,082 (74.9%) involving IMFs. During 2023, approximately 72,000, or nearly seven in 10, drug overdose deaths in the United States involved IMFs. Among these, carfentanil related deaths increased from 29 during January through June of 2023 to at least 238 during January to June of 2024.

Conclusion: The study utilized data from the CDC's State Unintentional Drug Overdose Reporting System (SUDORS) to demonstrate that the majority of fentanyl-related deaths in the United States involve illegally manufactured fentanyl.

Tanz L., et al. Detection of Illegally Manufactured Fentanyl and Carfentanil in Drug Overdose Deaths - United States, 2021 to 2024. **MMWR Morb Mortal Wkly Rep.** 2024; 73: 1099-1105.

HIP FRACTURE SURGERY AND MYOCARDIAL INJURY

Hip fractures are associated with significant morbidity and mortality, including cardiovascular related issues. The HIP ATTACK trial investigated whether accelerating surgery could improve outcomes in patients with hip fractures, especially among those presenting with myocardial injury.

The HIP ATTACK trial is an international, randomized, controlled trial involving 1,392 patients, 45 years of age or older, scheduled for hip fracture repair. Of these, 322 (23%) had elevated serum troponin levels at admission. The patients were randomly assigned to receive either accelerated surgery (with a median time of six hours from diagnosis to surgery) or standard care (a median of 24 hours). Outcomes were compared between those with and those without elevated troponin levels, and those with early and delayed surgical repair. Among patients with elevated troponin levels, the 90-day mortality in the early surgery group was better (10%) than that for those in the standard care group (23%). However, the benefits of accelerated surgery were not observed among patients with troponin levels in normal range.

Conclusion: This study of patients undergoing hip fracture repair found that, of those with elevated troponins on admission, surgical repair within 24 hours significantly reduced their risk of death within 90 days as compared to standard care.

Biccard, B., et al. Impact of Accelerated Surgery on Patients with Hip Fracture and Myocardial Injury: A Substudy of the HIP ATTACK Trial. **J Periop Med.** 2024; 69(3): 235-248.

THROMBOEMBOLISM AFTER FOOT AND ANKLE SURGERY

Venous thromboembolism (VTE) can be a life-threatening complication

following surgery. However, a lack of agreement persists concerning the use of VTE prophylaxis for foot and ankle surgery. This study was designed to better understand this issue.

This multicenter, prospective, national study involved 68 centers in the United Kingdom, coordinated by the British Orthopedic Foot and Ankle Society (BOFAS). Eligible patients were over 16 years of age, all undergoing foot and ankle surgery or repair of an Achilles tendon (TA) rupture. A lower limb VTE was diagnosed using Doppler ultrasound of all symptomatic patients and CT scan or CT pulmonary angiogram (CTPA) to confirm the presence of pulmonary embolism (PE). The primary outcome variables were symptomatic VTE and VTE-related mortality within 90 days of surgery. Data from the records of 11,363 patients were analyzed, with 99 cases of symptomatic VTE (0.87%) and VTE related mortality (0.03%) documented. Of the VTE prophylactics, the most commonly used was low molecular weight heparin (56%), followed by factor Xa inhibitors (6.7%) and aspirin (2.8%). The greatest risk of VTE was found in nonoperative TA ruptures (4.09%) and the lowest frequency in elective procedures (0.31%).

Conclusion: This large study of patients who underwent foot and ankle surgery found that the 90-day, post-operative incidence of symptomatic venous thromboembolism was 0.87%.

Mangwani, J., et al. UK Foot and Ankle Thromboembolism (UK-FATE) Audit Results. **Bone Joint J.** 2024, Nov 1;106-B (11): 1249-1256.

NIGHT SHIFT WORK AND BIOLOGICAL AGING

Shift work is increasingly common and has been linked to various health issues. This study explored the association between night shift work and accelerated biological aging.

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Data were obtained from the UK Biobank cohort, including 182,064 participants who provided detailed information about their work schedules. The participants were categorized as day workers, shift workers without night shifts, irregular night shift workers, or permanent night shift workers. Biologic aging was assessed using PhenoAge, calculated with the use of chronological age and nine blood biomarkers (albumin, creatinine, alkaline phosphatase, C- reactive protein, glucose, mean cell volume, red blood cell distribution width, white blood cell counts, and lymphocyte percentage). Data analysis was conducted on lifetime employment information for 51,455 subjects. Compared to day workers, shift workers without night shift, irregular night shift workers, and permanent night shift workers demonstrated increased biologic aging of 0.59, 0.87 and 1.30 years respectively ($p < 0.001$). In a model adjusted for risk factors, including BMI, the differences between biologic age and PhenoAge for shift workers without night shift, irregular night shift workers, and permanent night shift workers were 0.15 years, 0.28 years, and 0.54 years, respectively, suggesting that BMI mediated biologic age acceleration. In the fully adjusted model, those who had worked nightshifts for longer than 10 years showed the highest risk of biological ageing. **Conclusion:** This study found that night shift work contributes to biological ageing.

Shen, W., et al. Association of Night Shift Work and Biological Ageing: The Mediating Role of Body Mass Index. **Age and Ageing**. 2024, November; 53(11): afae242.

INPATIENT FALLS FOLLOWING POSTERIOR LUMBAR FUSION

Posterior lumbar fusion (PLF) is a common surgical remedy for a number of spinal pathologies. While the long-term outcome of these surgeries has been well studied, the incidence of postoperative inpatient falls (PIF) has not. This study was designed to better understand the rate and risk factors for PIF during hospitalization for PLF. Data were extracted from a large, national insurance claims data set that contains both inpatient and outpatient information from across the United States. Data were harvested from the records of all patients who

underwent single level PLF. Inpatient falls were identified using ICD9/10 codes. The data extraction also included patient characteristics, secondary injuries, length of stay, and hospitalization costs. The database review identified 342,890 patients undergoing single level PLF. Of these, inpatient falls were recorded for 4,379 patients (1.4%). A multivariate analysis was performed to determine factors independently associated with PIF, including active psychosis (odds ratio (OR) 3.35), active delirium (OR 2.83), history of falling (OR 2.47), commercial insurance (OR 1.59), Medicaid insurance (OR 1.4), dementia (OR 1.17), age (OR 1.12 per decade), and alcohol use disorder (OR 1.11). The average length of stay for those who fell was 12.3 days, compared to 5.3 days for those who did not fall ($p < 0.001$). **Conclusion:** This study of patients undergoing single level posterior lumbar infusion found that 1.4% experienced a fall during hospitalization, resulting in a significantly longer length of stay and increased costs.

Gouzoulis, M., et al. Rate and Risk Factors for Inpatient Falls following Single-Level Posterior Lumbar Fusion: A National Registry Study. **N Am Spine Soc J**. 2024, Aug 14; 20: 100549.

BLOOD FLOW RESTRICTION EXERCISE FOR KNEE OSTEOARTHRITIS

Up to 20% of patients who undergo total knee arthroplasties (TKA) report dissatisfaction with the procedure. Recently the use of blood flow restriction (BFR) has been explored as an adjunct to low load resistance training (LL-RT), as a means to strengthen the muscles surrounding a joint under much lower loads than required in traditional strengthening protocols. This study explored the efficacy of LL-RT, combined with BFR, as a treatment for patients dissatisfied with their TKA.

This prospective study included 45 patients who were more than six months post-TKA. The LL-RT (20% of the one repetition maximum) was performed twice per week for nine weeks. The BFR was obtained using individual limb occlusion pressure (LOP), defined as the minimum pressure needed to restrict arterial blood flow. Outcome measures included the EuroQol five-dimension

five-level questionnaire (EQ-5D-5L), the Knee Injury and Osteoarthritis Outcome Score (KOOS), the Knee Society Score: Satisfaction (KSSs), Pain Catastrophizing Scale (PCS), the six-minute walk test (6MWT), and the 30-Second Chair Stand Test (30CST).

At six weeks, compared to baseline, significant improvements were noted in KOOS subscales (pain, symptoms, ADLs, and QoL) and in the KSSs, EQ-5D-5L, and PCS. Two of the KOOS subscales met the minimal clinically important difference (MCID), including the QoL ($p=0.002$) and activities of daily living ($p<0.001$), as did the 6MWT ($p<0.001$), walking distance ($p<0.001$), and 30CST ($p<0.008$).

Conclusion: This study of patients dissatisfied with their primary total knee arthroplasty found that treatment with blood flow resistance exercise resulted in significant improvements in quality of life and function.

Stroobant, L., et al. Can Blood Flow Restriction Therapy Improve Quality of Life and Function in Dissatisfied Knee Arthroplasty Patients? **Bone Joint J.** 2024, Dec 1; 106-B (12): 1416-1425.

DEFERIPRONE FOR ALZHEIMER'S DISEASE

The FDA has recently approved lecanemab and donanemab for the treatment of Alzheimer's disease (AD). These monoclonal antibodies have been found to reduce plaque and modestly slow cognitive deterioration but also accelerate brain volume loss. As elevated iron level has been shown to increase neurodegeneration, this study explored the treatment efficacy of deferiprone, an iron chelator. Adults diagnosed with mild cognitive impairment or AD and brain β -amyloid pathology were randomized to receive twice daily oral deferiprone 15mg/kg or placebo for 12 months. Cognition was assessed at baseline and at six and twelve months using a neuropsychological test battery (NTB) of memory, executive function, and attention tasks. Outcomes were assessed using brain iron burden (BIB), determined by quantitative susceptibility mapping (QSM), magnetic resonance imaging, and brain volume changes. Fifty-four subjects completed the study. At 12 months, the MRI scans demonstrated that the deferiprone

group had decreased iron levels in the hippocampus, as compared with the placebo subjects ($p=0.03$). However, those in the deferiprone group demonstrated significantly worsened cognitive performance, as demonstrated by a faster decline in NTB z scores (-.80) compared to the placebo group (-.30; $p=0.002$). This seems to have been driven by worsening performance on executive function tests.

Conclusion: This study of patients with amyloid-confirmed mild cognitive impairment or early Alzheimer's disease found that deferiprone, 15 mg/kg twice a day, reduced brain iron burden and hippocampal iron but caused accelerated cognitive decline and increased regional brain atrophy.

Ayton, S., et al. Deferiprone in Alzheimer's Disease: A Randomized, Clinical Trial. **JAMA Neurol.** 2024, Nov. doi:10.1001/jamaneurol.2024.3733

GAIT ASSESSMENT USING WEARABLES

Deep brain stimulation of the subthalamic nucleus (STN-DBS) is a well-established surgical treatment for the management of the motor symptoms of Parkinson's disease (PD). As levodopa can improve specific gait parameters in these patients, this study assessed the effect of STN-DBS combined with levodopa on gait parameters using remote technology. This prospective study recruited patients with PD who presented for STN-DBS at the Movement Disorder Center of the IRCCS Istituto delle Scienze Neurologiche di Bologna from December of 2021 to February of 2024. The researchers employed wearable inertial measurement devices to assess gait and posture during combinations of medication and stimulation, including a) Stimulation On (StimOn)/Medication On (MedOn), b) StimOn/ MedOff c) StimOff/MedOn, d) StimOff/MedOff. During all conditions, gait analysis was completed including a 7 m timed walk, the Freezing of Gait Assessment Course (FoG-AC), and the Push and Release Test for postural stability. Wearable technology was used to record changes in gait parameters, including stride length, velocity, and stability, both before and six months after STN-DBS surgery. Compared to the StimOff/MedOff condition, the StimOn/MedOn

condition significantly improved gait speed ($p<0.001$), stride length ($p<0.001$), cadence($p=0.002$), and turning velocity ($p<0.001$). These improvements were greater than those of the MedOn/StimOff condition, as well as the MedOff/StimOn conditions.

Conclusion: This study of patients with Parkinson's disease used wearable gait monitors to demonstrate the positive effects of deep brain stimulation combined with levodopa on gait and postural parameters.

Cani, I., et al. Evaluating Gait and Postural Responses to Subthalamic Stimulation and Levodopa: A Prospective Study Using Wearable Technology. **Euro J Neurol.** 2025, Jan; 32(1): E16580.

BRAIN VOLUME AND BLAST RELATED MILD TRAUMATIC BRAIN INJURY

Recent advances in imaging have provided evidence that blast injuries are a unique mechanism of traumatic brain injury (TBI), with white matter (WM) alterations consistently associated with blast-related mild TBI (br-mTBIs). This study investigated the effect of br-mTBIs on regional brain volume. This prospective study included 774 US veterans and active-duty service members who participated in the Long-Term Impact of Military-Relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC). All participants had combat exposure, with 82% reporting one or more mild TBIs. Brain volume was measured using tensor-based morphometry on T1-weighted MRI scans. Cognitive performance was evaluated using measures of visual memory and learning, processing speed, mental flexibility, and working memory. Those with a history of br-mTBIs were compared to with those with no history of br-mTBIs (including uninjured individuals and those with non-blast-related mild TBI).

Compared to those with no br-mTBIs, those with a history of br-mTBIs had significantly smaller brain volumes in white matter and subcortical grey matter regions including the superior corona radiata, internal capsule, and globus pallidus. These volume differences were associated with poorer cognitive performance, particularly in working memory and processing speed.

Conclusion: This study of military personnel found that those with blast related mild traumatic brain injuries had long-term structural brain changes which were associated with reduced working memory and processing speed.

Dennis, E., et al. Differences in Brain Volume in Military Service Members and Veterans after Blast-Related Mild TBI: A LIMBIC-CENC Study. **JAMA Network Open.** 2024, Nov 11; 7(11): e2443416.

TERIPARATIDE, DENOSUMAB AND BIPHOSPHONATES FOR OSTEOPOROSIS

With the aging of the world's population, an increase is expected in age-related diseases including osteoporosis. Since the 1990s, bisphosphonates (BPs) have been the first line pharmaceutical treatment for osteoporosis. Since then, additional medical options have become available. This study compared the efficacy of teriparatide and denosumab to that of bisphosphonates.

This literature review scanned the published medical literature up to May 31, 2023. Eligible studies were head-to-head, randomized, controlled trials involving patients with osteoporosis, comparing those treated with BPs to those receiving either teriparatide or denosumab. The search identified 23 studies to include in the meta-analysis. Of these, 15 trials, involving 6,264 patients, assessed the risk of fracture. Those comparing parathyroid with BPs found that those treated with teriparatide had a greater reduction in fracture occurrence, with a relative risk (RR) of 0.61 ($p < 0.001$). The studies which compared denosumab and BPs found little difference in reductions in fractures (RR 0.99; $p = 0.96$). Studies which focused on the change in BMD found that, compared to treatment with denosumab, treatment with teriparatide resulted in greater improvement in BMD ($p = 0.001$).

Conclusion: This literature review and meta-analysis of medications used for the treatment of osteoporosis found that the reduction in the risk of fractures was greater among those treated with teriparatide, as compared to bisphosphonates and denosumab.

Li, M., et al. Efficacy and Safety of Teriparatide versus Bisphosphonates and Denosumab versus

Bisphosphonates in Osteoporosis Not Previously Treated with Bisphosphonates: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. **Arch Osteopor.** 2024; 19:118.

HYALURONIC ACID-BASED SCAFFOLD EMBEDDED WITH BONE MARROW ASPIRATE FOR CARTILAGE REPAIR

Articular cartilage injury tends to be progressive and can result in end stage joint failure requiring total joint arthroplasty. Hyaluronic based scaffolding, in association with bone marrow aspirate concentrate (HABMAC), is a one-step cartilage repair technique previously demonstrating successful clinic outcomes. This study reviewed the long-term outcomes of this procedure.

The subjects were 26 patients, ages 30 to 60 years, presenting with a grade four cartilage defect of $> 1 \text{ cm}^2$ located in the knee. All were treated with HA-BMAC between April of 2007 and January of 2022. A scaffold material consisting of a hyaluronic acid-based polymer was size matched to the defect. Then, the BMAC was clot-activated using batroxobin and placed into the defect, followed by the hyaluronic acid-based scaffold. The patients progressed from touchdown weightbearing to full weightbearing between weeks four and six. The patient outcomes were followed using a visual analog scale (VAS) and the Knee injury and Osteoarthritis Outcome Score (KOOS).

Twenty-six patients were available for analysis, including three with treatment failures and one who underwent medial compartment unicompartmental arthroplasty 12 years after HA-BMAC treatment. The survival rates of HA-BMAC cartilage repair, determined using Kaplan-Meier analysis, were 92.0% at five years, 88.0% at 10 years, and 88.0% at 16 years. The median VAS pain score was 0.6 at the final follow-up, reduced from a median of 5.0 preoperatively.

Conclusion: This study of patients with full thickness cartilage lesions at the knee found that a one-step repair using hyaluronic based scaffolding, in association with bone marrow aspirate concentrate, was successful in reducing pain and restoring function at 14 years.

Whyte, G., et al. One-Step Cartilage Repair of Full-Thickness Knee Chondral Lesions Using a Hyaluronic

Acid-Based Scaffold Embedded with Bone Marrow Aspirate Concentrate: Long-term Outcomes after a Mean Follow-Up Duration of 14 Years. **Am J Sport Med.** 2024, Dec; 52(14): 3561-3568.

FASCIOTOMY FOR CHRONIC EXERTIONAL COMPARTMENT SYNDROME

Deep posterior chronic exertional compartment syndrome (dp-CECS). This condition is characterized by deep calf pain, tightness, cramps, muscle weakness, and paresthesias. When conservative measures including resting, icing, and physiotherapy are unsuccessful, a fasciotomy may be considered. This prospective study evaluated the effectiveness of fasciotomy for deep posterior CECS and sought to identify factors predicting outcome.

The subjects were 74 patients diagnosed with unilateral or bilateral dp-CECS who underwent deep posterior fasciotomy. Patients rated symptoms at baseline, three months, and 12 months post-operatively. Outcome measures were patient-reported symptoms, patient-reported success, and return to sports.

Compared to baseline, total symptom scores at rest dropped by almost half at three- and 12-month follow-ups ($p < 0.001$). During exercise, total symptoms decreased more than 50% at three- and 12-month follow-ups ($p < 0.001$ for both). Three months after surgery, 63% had returned to sports of whom 25% returned to their preinjury level. Twelve months after surgery, 80% of the patients returned to sport with 28% returning to full sports activity. **Conclusion:** This study of patients with exertional compartment syndrome found that deep posterior fasciotomy was effective in reducing pain at rest and with exertion, although only 28% were able to fully return to sport after surgery.

van den Heuvel-Weiss, C., et al. Fasciotomy for Chronic Exertional Compartment Syndrome of the Deep Posterior Lower Leg Compartment: A Prospective Study. **Clin J Sport Med.** 2024; :10.1097/JSM.0000000000001298, November 22, 2024.

DEMENTIA ASSOCIATED WITH ANTICHOLINERGIC DRUGS

Previous studies have suggested that prolonged treatment with anticholinergic drugs is linked to long-

term cognitive decline and dementia. This study investigated the specific risk of dementia associated with different anticholinergic drugs. This nested, case-control design included records from the Clinical Practice Research Datalink (CPRD) GOLD database. From these records, patients 55 years of age or older who were diagnosed with dementia were matched with five individuals without dementia. The primary independent variable was the total cumulative use of anticholinergic drugs for the treatment of an overactive bladder. From the CPRD GOLD database 170,773 adults were identified with a diagnosis of dementia, with 804,385 matched controls. Anticholinergic drugs had been prescribed for nine percent of the dementia patients and 7.9% of the controls. The adjusted odds ratio (OR) for dementia associated with the use of anticholinergic drugs was 1.18. The increased risk was noted for those who used oxybutynin hydrochloride, solifenacin succinate, and tolterodine tartrate, while no increased risk was associated with the use of other anticholinergics, including darifenacin, fesoterodine fumarate, flavoxate hydrochloride, propiverine hydrochloride, and trospium chloride.

Conclusion: This large, population-based study found that the risk of dementia is increased with a greater cumulative use of specific anticholinergic drugs, but not with others.

Iyen, B., et al. Risk of Dementia Associated with Anticholinergic Drugs for Overactive Bladder in Adults Aged ≥ 55 Years: Nested, Case-Control Study. *BMJ Med.* 2024, Nov 12; 3 (1): e000799.

PONSEGROMAB FOR CANCER RELATED CACHEXIA

Cachexia is a common complication of cancer and is associated with an increased risk of death. As the GDF-15-GFRAL pathway has been identified as a modulator of anorexia, this study examined the therapeutic efficacy of Ponesegromab, a humanized monoclonal antibody that binds to circulating GDF-15 for the treatment of cachexia.

This randomized, double-blind, placebo-controlled, phase two trial was conducted at 74 sites in 11 countries. One hundred eighty-seven patients were randomly assigned to receive Ponesegromab at doses of 100 mg, 200 mg, or 400 mg, or a

placebo, administered subcutaneously every four weeks. The primary endpoint was the change in body weight from baseline to 12 weeks. At 12 weeks, significantly greater increases in body weight were found in all Ponesegromab groups compared to the placebo group. Compared to the placebo group, weight gain at 12 weeks was 1.22kg in the 100mg group, 1.92kg in the 200mg group, and 2.81kg in the 400mg group ($p < 0.05$ for all comparisons). Improvements in patient-reported outcomes were noted in the Ponesegromab groups, including reduced cachexia symptoms, improved appetite, physical activity, and increased skeletal muscle mass. No significant differences were noted between the groups in adverse events.

Conclusion: This study suggested that targeting GDF-15 with Ponesegromab may be a promising approach for managing cancer-related cachexia.

Groarke, J., et al. Ponesegromab for the Treatment of Cancer Cachexia. *N Engl J Med.* 2024, Dec 19; 391(24): 2291-2303.

CARDIOVASCULAR HEALTH IN RETIRED NFL PLAYERS

A number of studies have examined the health implications of playing football in the National Football League (NFL). As little data exist concerning the cardiovascular impact of the sport, this review was designed to better understand the cardiovascular health of former NFL players. Data were reviewed from PubMed, Embase, and Scopus databases for studies involving retired NFL players which addressed cardiovascular disease outcomes. The studies were categorized into four groups: weight gain and obesity, mortality, obstructive sleep apnea, and cardiovascular disease. From this review, 16 studies were identified with sample sizes ranging from 122 to 3,506 subjects. The data revealed that cardiovascular/cardiometabolic disease is the leading cause of death among retired NFL players. However, compared to the general population, retired NFL players had a decreased mortality. Compared to community matched controls, former NFL players had significantly lower prevalence of smoking and diabetes ($p < 0.01$), sedentary lifestyles ($p < 0.05$), and

metabolic syndrome ($p < 0.05$). Compared to community controls, a greater percentage of NFL players were at high risk for sleep apnea (27% versus 11.5%, respectively; $p = 0.002$).

Conclusion: This literature review indicates that former National Football League players have more favorable cardiovascular and metabolic profiles than community controls matched for body mass index, ethnicity, and age.

Sisk, M., et al.. Cardiovascular Disease in Retired NFL Players: A Systematic Review. *Physician Sports Med.* 2024, Oct; 52(5): 444-451.

DIETARY PATTERNS TO PROMOTE CARDIOMETABOLIC HEALTH

The global prevalence of cardiovascular disease (CVD) continues to rise, substantially influenced by dietary choice. This review investigated the effect of the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet, the carbohydrate restricted diet, and Time Restricted Eating (TRE) on cardiometabolic health.

This literature review focused on studies of various dietary patterns through observational studies, clinical trials, and meta-analyses. The Lyon Diet Heart Study involved patients who were post-myocardial infarction, finding that, as compared to controls, the incidence of cardiac death and myocardial infarction were significantly reduced by greater $> 70\%$ in those consuming the Mediterranean Diet. The CARDIOPREV randomized, controlled trial involving patients with CHD found a 30% reduction in myocardial infarction, stroke, or cardiovascular death among those consuming a Mediterranean diet. The DASH dietary pattern has been found to reduce systolic blood pressure, diastolic blood pressure, and other risk factors, with RCTs lacking outcomes of stroke or heart disease. Studies of low carbohydrate diets demonstrated greater weight loss and lower plasma triglyceride levels compared with higher-carbohydrate diets. Studies of intermittent fasting have varied from alternating 24-hour periods of fasting with 24 hours of eating to eating only within an eight- to 10-hour interval each day. The benefits of this

approach on cardiovascular outcomes are not yet clear.

Conclusion: This literature review found strong evidence that the Mediterranean diet can reduce the risk of cardiac death and myocardial infarction, and that the DASH diet and intermittent fasting are lacking in strong evidence of improved cardiovascular or cerebrovascular outcomes.

Pagidipati, N., et al. Dietary Patterns to Promote Cardiometabolic Health. **Nat Rev Cardiol**, 2025, January; 22: 38-46.

HOME-BASED MONITORING OF CEREBRAL OXYGENATION IN ORTHOSTATIC HYPOTENSION

Orthostatic hypotension (OH) is prevalent among older adults, ranging from six percent in the general population to 26% in adults 85 years of age or older. This study investigated the utility of at-home cerebral oxygenation measures to assist with the monitoring of OH. This study involved 21 participants, divided into two groups: 10 with OH (mean age 77) and 11 without OH (mean age 78). The subjects wore a portable near-infrared spectroscopy (NIRS) sensor for two days, 10-11 hours per day. The sensor measured cerebral oxygenation during three standardized supine-stand tests daily and during unsupervised daily activities. The differences in cerebral oxygenation responses were calculated between those with and those without OH, as well as symptomatic versus asymptomatic postural changes. Data collection also involved continuous BP monitoring with volume-clamp photoplethysmography during controlled supine-stand transitions, with additional daily activities captured via accelerometers and diaries.

The NIRS method proved feasible, with oxygenation parameters derived from standardized supine-stand tests at home were found to be similar to those in the laboratory setting. In addition, differences in cerebral oxygenation were found between OH and non-OH groups. OH participants showed lower oxygen recovery than did those without OH. However, the reliability of NIRS measurements showed only moderate consistency across repeated tests, suggesting variability in orthostatic responses.

Conclusion: This study indicates that NIRS could potentially be a useful tool for monitoring OH in daily life, providing insights into cerebral oxygenation not captured by BP alone.

Klop, M., Et Al. Home-Based Monitoring of Cerebral Oxygenation in Response to Postural Changes Using Near-Infrared Spectroscopy. **Geroscience**. 2024, Dec; 46(6): 6331-6346.

ADIPOCYTES AND FIBROBLASTS IN INFLAMMATORY ARTHRITIS

In osteoarthritis (OA) and rheumatoid arthritis (RA), the synovium (tissue lining the joint) loses adipocytes (fat cells) and gains more inflammatory and fibrotic tissue. This study explored the influence of adipocytes on the behavior of the fibroblasts that produce connective tissue in healthy versus diseased synovium.

Tissue was harvested from synovial tissues of recently deceased adults with no known knee issues. These were compared to tissue from patients with inflammatory arthritis. From these, adipocytes and fibroblasts were co-cultured to assess the impact on fibroblast behavior. Genetic manipulation techniques (CRISPR/Cas9) were used to knock out glucocorticoid receptors in adipocytes to assess the impact on fibroblast behavior. The gene expression was then analyzed through RNA sequencing and histological methods. The healthy synovial tissue showed gene signatures related to lipid transport and metabolism, which were not present in arthritis samples. When fibroblasts from the tissue of patients with RA were treated with a medium conditioned by fat cells, they regained a healthy gene profile. Subsequent analysis identified cortisol as a key factor in this medium, and its addition to RA fibroblasts mimicked the healthy gene expression pattern, whereas glucocorticoid receptor antagonists reversed this effect.

Conclusion: This study demonstrates that adipose tissue and cortisol signaling are important contributors to healthy synovial tissue and that a loss of adipocytes in arthritis leads to a loss of this healthy fibroblast phenotype.

Faust, H., et al. Adipocyte Associated Glucocorticoid Signaling Regulates Normal Fibroblast Function, Which Is

Lost in Inflammatory Arthritis. **Nat Commun**. 2024, Nov 14; 15: 9859.

GENETIC OVERLAP OF OSTEOARTHRITIS AND CARDIOVASCULAR DISEASE

A recent study found that the risk of cardiovascular disease was greater by 12 to 37% among patients with osteoarthritis than among the general population. It is unknown to what extent these disorders share a common genetic etiology. This study explored the genetic overlap between these two diseases. Data were obtained from the Swedish twin registry, a national registry including more than 194,000 Swedish twins. These data were linked to the actual patients registered in 2017 to extract the diagnostic codes for musculoskeletal disease and cardiovascular disease from 1997 through 2016. Data were obtained from twins ≥ 18 years of age in 1997, with a minimum follow-up of one year.

Data were obtained from 59,970 twins in 29,985 twin pairs. In total, 7,363 individuals had OA in any joint (938, 2,498, and 3,845 in the hand, hip, and knee joints, respectively). Also, 13,685 had arrhythmias, 6,560 CHD, 2,724 heart failure, and 4,730 stroke). The crude phenotypic correlation (r_{PT}) between any site OA and any of the severe CVDs was 0.16, indicating common etiological influences. The MZ cross-twin correlation ($r_{MZ}=0.16$) was equally high as the phenotypic correlation, yet higher than the DZ cross-twin-cross trait correlation ($r_{DZ}=0.11$), indicating that genetic factors are of importance in the shared etiology.

Conclusion: This study of nearly 60,000 twins found that a significant portion of the correlation between OA and severe CVD in an individual can be explained by genetic factors shared for the two diseases.

Magnusson, K., et al. Shared Genetic Factors between Osteoarthritis and Cardiovascular Disease May Underlie Common Etiology. **Nature Commun**. 2024, 15: 9569.

EARLY AEROBIC EXERCISE AND MUSCULOSKELETAL INJURIES AFTER SPORT-RELATED CONCUSSION

Research has demonstrated that aerobic exercise (AE), prescribed two to 10 days after a sports related concussion (SRC), can safely

facilitate return to school and sports faster than stretch or strict rest. This study investigated the effect of AE following concussion on subsequent musculoskeletal (MSK) injuries. This multicenter study recruited adolescents at three community and hospital-affiliated sports medicine concussion centers. Eligible subjects presented within 10 days of a SRC and were randomly assigned to either an AE group (n=38) or a control group engaged in stretching exercise (n=25) at least 20 min daily, for up to four weeks. The AE was tailored to each participant's heart rate threshold (HRT), as determined by the Buffalo Concussion Treadmill Test (BCTT). At three-months follow-up, the participants completed follow-up questionnaires to document MSK injuries, return to school and sport, and subsequent concussions. At a mean follow-up time of 129.5 to 126.7 days, MSK injuries were reported by 5.3% of the AE group and 24% of the stretching group (p=0.05). No significant differences were observed in the time to return to school or sport, or the incidence of subsequent concussions. When controlling for exposure duration and return to preinjury sport participation levels, participants in the stretch/control group were found to be 6.4 times more likely to suffer an MSK injury than were those in the AE group.

Conclusion: This prospective study of adolescent athletes with sports related concussion found that targeted aerobic exercise resulted in significantly fewer musculoskeletal injuries after return to sport, as compared to a control condition.

Leddy, J., et al. Early Targeted Heart Rate Aerobic Exercise Reduces Proportion of Subacute Musculoskeletal Injuries after Recovery from Sport-Related Concussion. *Clin J Sport Med.* 2024, Nov.1; 34(6): 509-516.

REHABILITATION OF VISUAL FIELD DEFECTS WITH TRANSCRANIAL DIRECT CURRENT STIMULATION

Homonymous visual field defects (HVFDs) after acquired brain injuries can significantly hinder daily activities. Rehabilitation for HVFDs is based on restitutive and compensatory strategies. This study was designed to determine whether transcranial direct current stimulation (tDCS) can increase the effectiveness of compensatory training for HVFDs.

The subjects were 18 adults 28-73 years of age with chronic VFDs secondary to brain injury. All received compensatory multisensory (audiovisual) training, two hours per day for ten days. Concurrent with training the subjects were randomly assigned to one of three groups: ipsilateral occipital tDCS (IO), ipsilateral parietal tDCS (IP), or sham tDCS (S). Before and immediately after each training session, as well as one and four months after completion of training, participants carried out a visual detection task, and two visual search tasks (EF and Triangles search tests). The accuracy (ACC) and response times (RT) were analyzed.

For the EF test, ACC analysis found no significant effects of tDCS session (p=0.985). However, the RTs improved with tDCS (p<0.001) with greater improvement noted in the IO group (p<0.001). For the Triangles search test, RTs were faster in the IO group (p<0.001) and IP group (p<0.001) than the S group.

Conclusion: This study of patients with chronic homonymous visual field defects found that the effects of compensatory multisensory (audiovisual) training was enhanced by the use of ipsilateral occipital transcranial direct current stimulation.

Diana, L., et al. Enhancing Multisensory Rehabilitation of Visual Field Defects with Transcranial Direct Current Stimulation: A Randomized Clinical Trial. *Eur J Neurol.* 2025;32: e16559.

CORRECTING SEVERE HYPONATREMIA DURING HOSPITALIZATION

U.S. and European clinical practice guidelines for correcting hyponatremia recommend limiting serum sodium correction to <10 to 12 mEq/L in any 24-hour period and <18 mEq/L in any 48-hour period. As recommendations were based on low-quality evidence, this study was designed to help clarify safest and most effective correction strategies for this condition.

A comprehensive literature search was completed across multiple databases including PubMed, Embase, and the Cochrane Library to identify relevant studies published up to March 2023. Sixteen studies were chosen that reported on the correction of hyponatremia in adults. A meta-analysis was completed using the data from the 16 studies involving 11,811 patients with a mean

age of 68 years. Four correction-rate categories were identified, including: Very rapid: >12 mEq/L per 24 hours, Rapid: >8 to 10 mEq/L per 24 hours, Slow: 6 to 10 mEq/L per 24 hours Very slow: <4 to 6 mEq/L per 24 hours. Compared with slow and very slow correction, rapid correction was associated with 32 and 221 fewer in-hospital deaths per 1000 treated patients. In addition, compared with slow and very slow correction at 30 days, rapid correction was associated with 61 and 134 fewer deaths per 1000 treated patients. Lengths of stay were shorter, by 1 day and 3 days, after rapid correction than after slow and very slow correction.

Conclusion: In this systematic review and meta-analysis, slow correction and very slow correction of severe hyponatremia were associated with an increased risk of mortality and increased hospital length of stay compared to rapid correction.

Ayus, J., et al. Correction Rates and Clinical Outcomes in Hospitalized Adults with Severe Hyponatremia. A Systematic Review and Meta-Analysis. *JAMA Intern Med.* 2025 Jan 1;185(1):38-51. doi: 10.1001/jamainternmed.2024.5981.

GABAPENTINOIDS AND HIP FRACTURE

Gabapentinoids have been marketed as a safe alternative to opioids for the treatment of neuropathic pain. Gabapentinoids are actively transported across the blood brain border, explaining their central nervous adverse events including somnolence, dizziness, gait disturbance, and balance disorder. As these may increase the risk of falling, this study investigated the association between gabapentinoids and the risk of hip fractures across age groups, frailty status, and history of chronic kidney disease (CKD). Data were obtained from four Australian national datasets including the Victorian Admitted Episodes Dataset (VAED), the Victorian Emergency Minimum Dataset (VEMD), Pharmaceutical Benefits Scheme (PBS), and the National Death Index (NDI). Data were extracted from the records of patients 50 years of age or older, admitted for a first hip fracture, and with at least one prescription for gabapentinoids, between March 2013 and June 2018. The analysis included: (1) the case crossover analysis and (2) the future-case-control case-crossover analysis.

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Patient frailty status was assessed using the Hospital Frailty Risk Score (HFRS).

During the study, 29,293 patients were hospitalized for a first hip fracture. Of these 2,644 adults ≥ 80 years of age were dispensed gabapentinoids before hospital admission and were matched with a control. Gabapentinoid use was associated with increased odds of hip fractures (Odds Ratio (OR), 1.96). The risk was higher for those with elevated HFRS (OR 1.75) compared to low HFRS (1.26) as well as those with CKD (OR 2.41), compared to those without CKD (1.25).

Conclusion: This study of elderly Australian residents found that the use of gabapentinoids was associated with an increased risk of hip fracture.

Leung, M., et al. Gabapentinoids and Risk of Hip Fracture. **JAMA Network Open.** 2024;7(11):E24444488.Doi.

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