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Tai Chi Is More Effective Than Balance and Strengthening Exercises for Fall Prevention

In high-risk elders, tai chi lowered the rate of falls substantially.

Falls in older adults often are preventable with proper training. In this study, researchers in Oregon randomized 670 older adults (mean age, 78; mostly white women) at high risk for falling to one of three interventions:

- Tai ji quan (better known as tai chi)
- Multimodal exercise that incorporates strengthening, aerobic training, balance training and flexibility exercises
- Stretching (control group)

All interventions consisted of 60-minute sessions, held twice weekly for 24 weeks, with progressively increasing intensity as participants adapted. The cost per person for either tai chi or multimodal exercise was roughly US\$900. At 6-months the tai chi group experienced significantly fewer falls than the multimodal



group and the control group (11 vs. 16 and 27 falls/100 person-months). No serious adverse events were associated with the interventions.

COMMENT: The multimodal exercise intervention has been the commonly accepted standard for fall prevention, but these results suggest tai chi is superior.

CITATION(S): Li F et al. Effectiveness of a therapeutic tai ji quan intervention vs a multimodal exercise intervention to prevent falls among older adults at high risk of falling: A randomized clinical trial. JAMA Intern Med 2018 Sep 10; [e-pub]. (<https://doi.org/10.1001/jamainternmed.2018.3915>)

JAMA Netw Open 2018 Sep 14; 1:e182327

Omega-3 Dietary Supplements Might Alleviate Some Anxiety Symptoms

In a meta-analysis, daily ω -3 dosages ≥ 2000 mg yielded modest positive clinical effects.

Dietary supplements containing ω -3 polyunsaturated fatty acids (PUFAs) — both eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) — are purported to alleviate anxiety symptoms. In this meta-analysis, researchers identified 19 randomized trials (16 placebo controlled; 2240 total patients; mean patient age, 42) in which benefits of ω -3 PUFA supplements (mean dosage, ≈ 1600 mg/day) were evaluated in a wide array of anxiety diagnoses and conditions.

Findings of the meta-analysis included the following:

- Anxiety symptoms declined from baseline in patients who received ω -3 PUFAs, although the clinical effect was modest.
- The association with fewer anxiety symptoms occurred only in patients with defined clinical anxiety diagnoses and not in patients with nonspecific anxiety symptoms.
- The association with fewer anxiety symptoms was noted only for daily ω -3 PUFA dosages ≥ 2000 mg and only when the proportion of EPA in the ω -3 PUFAs was $\geq 60\%$.

COMMENT: These findings give clinicians some guidance when patients ask whether ω -3 PUFA supplements are useful for diagnosed anxiety. However, this benefit is modest, and other proposed benefits, particularly for preventing cardiovascular disease, are unproven.

CITATION(S): Su K-P et al. Association of use of omega-3 polyunsaturated fatty acids with changes in severity of anxiety symptoms: A systematic review and meta-analysis. JAMA Netw Open 2018 Sep 14; 1:e182327. (<https://doi.org/10.1001/jamanetworkopen.2018.2327>)

Lancet 2018 Sep 22; 392:1015



Does Moderate Alcohol Consumption Confer Health Benefits?

It probably depends on the underlying distribution of diseases in a given population.

Epidemiologic research conducted in developed nations has shown that moderate alcohol consumption — 1 to 2 drinks daily in men, and 1 drink daily in women — confers overall health benefits. In these studies, one drink generally is defined as consumption of 10 g of pure ethyl alcohol.

In the Global Burden of Diseases study, data were collected from developed and developing nations. Researchers report that all-cause and cancer-related mortality increase linearly with alcohol use, with no protective effect from moderate consumption. However, an apparent protective effect of moderate alcohol intake against ischemic heart disease was noted.

COMMENT: Some media coverage of this research claimed that the study disproved past advice on the health benefits of moderate alcohol intake. In my opinion, that is not the case. Past advice was predicated on moderate alcohol consumption's protective effect against vascular diseases, the chief causes of death in *developed* nations, and the results of this new study are consistent with that. The causes of death in *developing* nations are different: For example, in this study, tuberculosis (TB) was the major cause of death in young adults — showing the influence of mortality data from developing nations on the overall data set — and alcohol probably raises risk for TB reactivation. For our patients in developed nations, except for those with personal or family histories of breast (and possibly other) cancers, the vascular benefit of moderate alcohol intake still appears to offset potential harms.

CITATION(S): GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990–2016: A systematic analysis for the Global Burden of Disease study 2016. Lancet 2018 Sep 22; 392:1015. ([https://doi.org/10.1016/S0140-6736\(18\)31310-2](https://doi.org/10.1016/S0140-6736(18)31310-2))

N Engl J Med 2018 Sep 27; 379:1244

Spinal Cord Stimulation for Standing and Walking After Complete, Chronic, Traumatic Spinal Cord Injury

With electrical stimulation and intensive training, patients had improvements in function.

In a partially manufacturer-supported trial, four patients with chronic motor paralysis after traumatic spinal cord injury underwent epidural stimulation and intense rehabilitation in standing and stepping. Treatment with stimulation began at least 2 years after their injury. All four patients had complete paralysis from trauma in the cervical or thoracic regions. Intensive physical therapy alone, 10 hours per week for up to 9 weeks, did not result in motor movement, confirmed by electromyography.

A 16-electrode array was implanted epidurally over L1 to S1-2 and was set to activate lower extremity muscles. Several weeks after implantation, different muscles groups were activated by stimulating each



epidural anode and cathode to determine combinations that effectively stimulate walking. Participants underwent 1-hour training sessions one to two times per day.

Two participants walked over ground with assistance device; one of these was independent using two poles after 278 sessions over 85 weeks and the other first transitioned to over-ground walking after 81 sessions over 15 weeks. The first patient was able to walk 90 meters without rest. The other two patients progressed to stepping on a treadmill with body-weight support and sitting and standing independently. With the stimulator off, the legs were once again paralyzed.

COMMENT: Patients with complete paralysis had clear and significant functional gains with spinal cord stimulation and intensive training. The authors speculate that spinal cord interneurons are being stimulated because of the standing and stepping patterns of muscle recruitment. The treatment involves an invasive device with epidural electrodes, in addition to a very intense training program. We can hope that the device and training will improve and become available to more people.

CITATION(S): Angeli CA et al. Recovery of over-ground walking after chronic motor complete spinal cord injury. *N Engl J Med* 2018 Sep 27; 379:1244. (<https://doi.org/10.1056/NEJMoa1803588>)

Neurology 2018 Sep 18; 91:558

Lumbosacral Radiculopathy Syndrome Is a Work-Related Disease

Exposure to occupational risk factors is strongly related to lumbosacral radiculopathy syndrome.

Low back pain is a major public health issue and cause of disability. Among the working population, it has a major socioeconomic impact. Occupational exposure including hard work, frequently bending or twisting, standing up, sitting, and concentration demands are risk factors for low back pain (*Occup Environ Med* 1997; 54:741). Prevalence of low back pain has reportedly increased more than 100% in the last decade and ranges from 6% to 45% in various countries (*F1000Research* 2016; 5:1530). The overall objective of this review and dose-response meta-analysis was to determine whether lumbosacral radiculopathy syndrome can be attributed to work.

The authors performed a systematic review in PubMed and Embase. Individuals with lumbosacral radiculopathy syndrome (LRS) diagnosed by clinicians were included, and workers exposed to work-related risk factors were compared with workers less or more exposed. Of 7350 references assessed, 24 studies met the inclusion criteria, with a total of 10,142 participants. Of the studies, 13 were included in the meta-analysis, 5 rated as having low risk of bias and 8 as having high risk of bias. The meta-analysis showed significant associations between physically hard work, lifting and carrying, or bending or twisting of the



trunk and LRS diagnosis. The combination of lifting and bending conferred the highest risk for LRS. No significant associations were seen for professional driving or sitting. A dose-response relationship per 5 years of exposure was seen for bending, lifting, and the combination of bending and lifting.

COMMENT; This well-conducted study provides significant evidence that LRS can be classified as a work-related disease, particularly depending on the exposure to bending of the trunk, lifting, and carrying. There was not a significant association between professional driving or sitting and LRS. To prevent LRS, policies must be established to prevent work-related risk factors.

CITATION(S): Kuijer PPFM et al. Work-relatedness of lumbosacral radiculopathy syndrome: Review and dose-response meta-analysis. *Neurology* 2018 Sep 18; 91:558.
(<https://doi.org/10.1212/01.wnl.0000544322.26939.09>)

Lancet Neurol 2018 Oct 1; 17:870

Multiple Sclerosis with Reduced Neuronal Densities and Lack of Cerebral Demyelination

Myelocortical multiple sclerosis appears to be due to degeneration of neurons.

Multiple sclerosis (MS) is an autoimmune demyelinating disease characterized by white matter plaques with variable loss of axons. Investigators evaluated the pathologic characteristics of patients who appeared not to have demyelinating white matter lesions at autopsy.

Of 100 patients with MS who underwent autopsy, 12 had no visible white matter lesions on gross inspection of 1 cm slices; these patients were classified as having myelocortical MS (mMS). The mMS cases were matched with 12 individuals with typical MS (tMS), based on visible white matter lesions at autopsy.

The most common clinical phenotype in mMS was secondary progressive MS, but relapsing remitting and primary progressive MS were also represented. Cerebral white matter lesion area in mMS was 0.4 cm² per hemisphere — much less than the 14.14 cm² in tMS. In the spinal cord, demyelination occupied 3.8% of the area per patient in mMS versus 13.8% in tMS. Subpial lesions were fewer in mMS as well, occupying 4.5% per patient compared with 9.7% for tMS. Neuronal density was reduced in layers III, V, and VI in mMS, but only in layer V in tMS, compared with healthy controls. Imaging parameters suggested a trend toward fewer T2 and T1 lesions in mMS. Investigators found similar measures in brain parenchyma fraction between mMS and tMS, and slightly increased cortical thickness in mMS compared with typical MS. Despite matching MRI T2-weighted lesions in mMS to the brain slices, the authors found no demyelination in those regions.

COMMENT: At autopsy, a small proportion of MS patients appeared to have neuronal degeneration without concomitant demyelinating disease. These mMS patients appeared similar to those with tMS in disease course and MRI findings. This study raises the question as to whether all MS is the same. Perhaps some patients have a primary neurodegenerative condition. Alternatively, neuronal degeneration may exist on a continuum, with cerebral-white-matter-dependent and independent pathways.



CITATION(S): Trapp BD et al. Cortical neuronal densities and cerebral white matter demyelination in multiple sclerosis: A retrospective study. *Lancet Neurol* 2018 Oct 1; 17:870. ([https://doi.org/10.1016/S1474-4422\(18\)30245-X](https://doi.org/10.1016/S1474-4422(18)30245-X))

JAMA Neurol 2018 Aug 13

Hemorrhage Risks from Specific NOACs Compared with Aspirin

Higher-dose rivaroxaban was associated with an increased risk for intracranial hemorrhage compared with aspirin.

Oral anticoagulation is beneficial for stroke patients with confirmed atrial fibrillation, but when a cardioembolic source is merely suspected but not proven, the picture is less clear. Any potential role of non-vitamin K antagonist oral anticoagulants (NOACs) to treat embolic stroke of undetermined source (ESUS) is critically dependent on the specific risk for intracranial hemorrhage associated with each NOAC compared with standard aspirin therapy.

Therefore, investigators performed a partially industry-funded systematic review and meta-analysis of randomized clinical trials to compare the hemorrhage risks of specific NOACs with that of aspirin. The analysis included 5 randomized trials totaling 39,398 participants. No trials directly comparing dabigatran or edoxaban to aspirin were available.

A 15-mg to 20-mg daily dose of rivaroxaban was associated with a significantly increased risk for intracranial hemorrhage compared with aspirin, but a 10-mg daily or 5-mg twice daily dose of rivaroxaban and a 5-mg twice daily dose of apixaban were not. No similar analysis of dabigatran or edoxaban was possible, although an exploratory analysis based on indirect comparisons suggested that dabigatran and edoxaban had similar intracranial hemorrhage risks as aspirin.

COMMENT: These results were principally driven by NAVIGATE-ESUS (*NEJM JW Neurol Jul 2018* and *N Engl J Med* 2018; 378:2191), which was terminated prematurely for excess bleeding events and for futility: Symptomatic intracranial hemorrhage occurred in 20 of 3609 patients in the rivaroxaban 15-mg group versus 5 of 3604 patients in the aspirin group. Similar trials of dabigatran (RE-SPECT ESUS; NCT02239120) or apixaban (ATTICUS; NCT02427126) versus aspirin for ESUS and apixaban versus aspirin for atrial cardiopathy (ARCADIA; NCT03192215) are ongoing or not yet published. A comparative effectiveness study directly comparing NOACs would be clinically useful. But given the high costs to conduct such a study and the risk that a particular drug will be shown to be inferior to the others, active support from drug makers for such an effort seems unlikely. In the meantime though, caution is warranted for any efforts to expand the use of higher-dose rivaroxaban to stroke patients with a suspected embolic source, but not proven atrial fibrillation.

CITATION(S): Huang W-Y et al. Association of intracranial hemorrhage risk with non-vitamin K antagonist oral anticoagulant use vs aspirin use: A systematic review and meta-analysis. *JAMA Neurol* 2018 Aug 13; [e-pub]. (<https://doi.org/10.1001/jamaneurol.2018.2215>)



Gastrointest Endosc 2018 Sep 14

EUS-Guided Photodynamic Therapy for Locally Advanced Pancreatic Cancer

A small phase 1 study establishes hope for better tumor necrosis.

Despite improvements in many areas, pancreatic cancer still carries a dismal survival rate. A recent phase 1 trial evaluated endoscopic ultrasound-guided photodynamic therapy (EUS-PDT) in 12 patients with locally advanced pancreatic cancer.

All patients received an injection of a photosensitizing agent (porfimer sodium) 2 days prior to undergoing EUS-PDT. During the procedure, a 19-gauge needle was used to access the tumors, and a light-diffuser catheter was passed into the target tumors; PDT was delivered using 630 nm laser light. CT scan 18 days after PDT was done to assess for change in pancreatic necrosis. Nab-paclitaxel and gemcitabine were initiated 1 week after the CT and given until disease progression or significant toxicity developed.

Compared with baseline scans, follow-up imaging showed increased volume and percent of tumor necrosis in 6 of 12 patients. By RECIST criteria, progressive disease developed in 6 of 12 patients, stable disease was seen in 3 of 12, partial response was seen in one, and response was not evaluable in two. Adverse events were largely related to the photosensitizing agent and chemotherapy.

COMMENT: These phase 1 results confirm at least the preliminary safety of EUS-PDT in patients with pancreatic cancer. Given the limited susceptibility of most pancreatic cancers to chemotherapeutic agents, a technology that could increase tumor necrosis warrants serious evaluation and further study. For patients with limited options, EUS-PDT may be worth considering. Treatment protocols and techniques need further investigation so that optimal approaches can be identified.

CITATION(S): DeWitt JM et al. Phase I study of EUS-guided photodynamic therapy for locally advanced pancreatic cancer. Gastrointest Endosc 2018 Sep 14; [e-pub]. (<https://doi.org/10.1016/j.gie.2018.09.007>)

Pediatrics 2018 Sep 17

Supporting Transgender and Gender-Diverse Youth

AAP policy statement includes recommendations about approaches that pediatric health providers should follow when caring for TGD youth.

Transgender and gender-diverse (TGD) youth experience disparities regarding access to physical and mental health resources; moreover, pediatric providers often do not feel skilled at caring for these patients. A recent policy statement from the American Academy of Pediatrics (AAP) provides a comprehensive summary of appropriate terms, explanations of medical interventions, and recommendations for optimizing the well-



being of TGD youth and their parents. This evidence-based statement is supported by the expert opinion of clinical and research leaders.

The statement outlines caregiving challenges and provides management suggestions for promoting positive development while preventing the stigma and discrimination that these youth face. A gender-affirmative care model is recommended as the “gold standard,” in which all pediatric providers and staff take responsibility for helping patients feel welcome, safe, and accepted. The benefits of a multidisciplinary clinic are noted, with treatment approaches adjusted in accord with pubertal development.

COMMENT: Increasing numbers of TGD youth and their families are presenting to pediatric providers for education, care, and referrals. Thus, an urgent need has arisen for relevant formal training of clinicians, standardized treatment protocols, and more data on safety and medical outcomes to guide clinical practice. Care of the TGD child or adolescent is a rapidly growing clinical field that warrants immediate attention from pediatricians. As mental health consequences — including suicide — occur at disturbing rates among TGD adolescents, health providers play important front-line roles. Pediatric providers can and should advocate for better medical care, while assuring that mental health services are provided in a timely and comprehensive manner.

CITATION(S): Rafferty J et al. Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. *Pediatrics* 2018 Sep 17; [e-pub]. (<https://doi.org/10.1542/peds.2018-2162>)

J Pediatr 2018 Aug 29

Automated Urinalysis Not Sufficient to Diagnose UTI

Evaluation of automated urinalyses in over 2500 children younger than 2 years of age found that bacteriuria without pyuria was unlikely to represent a urinary tract infection.

Whether the presence of bacteriuria on an automated urinalysis is diagnostic for urinary tract infection (UTI) in children has remained controversial.

A retrospective study of 2554 children aged <2 years (median, 6.1 months) seen in a children's hospital emergency room compared the results of automated urinalysis paired with urine cultures in diagnosing UTI; 19% of the sample had positive urine cultures.

The number of bacterial colonies on culture increased with the concentration of microscopic bacteriuria (graded as negative, trace, 1+ to 3+). With a bacterial count of 1+ or more, 60% had pyuria (5 or more white blood cells per high-power field). Among the urinalyses with isolated bacteriuria without pyuria (8%), only 10% had a positive culture. The positive predictive value (PPV) of pyuria and bacteriuria of 1+ or more was 80%, compared 52% for bacteria alone or 36% for pyuria alone. Urine concentration influenced the results. The likelihood of a UTI was three times greater with a reading of 1+ bacteriuria in dilute urines <1.015 specific gravity compared with more concentrated urines



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COMMENT: The new findings in this study are that automated microscopic bacteriuria alone is not a good screening test for a positive urine culture. Use of the dipstick nitrite and leukocyte esterase is valuable but not as sensitive as the presence of microscopic bacteriuria with pyuria. Diagnosis of UTI requires evaluation of the patient as well as the urinalysis and culture. The presence of asymptomatic bacteriuria without pyuria is unlikely to be a UTI.

CITATION(S): Chaudhari PP et al. Microscopic bacteriuria detected by automated urinalysis for the diagnosis of urinary tract infection. J Pediatr 2018 Aug 29; [e-pub].
(<https://doi.org/10.1016/j.jpeds.2018.07.007>)

