GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Does Vitamin D Supplementation Have a Role in the Treatment of Adult Depression?

Does Vitamin D Supplementation Have a Role in the Treatment of Adult Depression?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Effect of Long-term Vitamin D_3 Supplementation vs Placebo on Risk of Depression or Clinically Relevant Depressive Symptoms and on Change in Mood Scores: A Randomized Clinical Trial

Okereke OI, Reynolds CF, Mischoulon D, et al. Effect of Long-term Vitamin D_3 Supplementation vs Placebo on Risk of Depression or Clinically Relevant Depressive Symptoms and on Change in Mood Scores: A Randomized Clinical Trial. *JAMA*. 2020; 324(5):471–480. doi:10.1001/jama.2020.10224

KEY TAKEAWAY: Vitamin D_3 supplementation in adults 50 years and older at risk for depression but without relevant symptoms at baseline did not prevent incident or recurrent depression.

STUDY DESIGN: RCT

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Low levels of vitamin D is hypothesized to play a role in depression risk along with the etiology of seasonal affective disorder. There have been numerous small studies examining vitamin D supplementation on depression; however, no studies have simultaneously examined supplementation on prevention of incident and recurrent depression.

PATIENTS: Adults 50 years and older at risk for incident or recurrent depression

INTERVENTION: 2,000 IU/day vitamin D (+/- fish oil) supplementation

CONTROL: Placebo

OUTCOME: Total risk of depression

Secondary Outcome: Incident and recurrent depression

METHODS (BRIEF DESCRIPTION):

- Participants annually mailed study questionnaires including PHQ-8 depression scale.
- Adjusted mean PHQ-8 scores compared annually.
- Exclusion criteria: clinically relevant depressive symptoms for 2 or more weeks in past 2 years, alcohol or substance use disorder, or major psychiatric conditions
- In-person psychiatric evaluations conducted in a subset to validate results.
- Serum 25-hydroxyvitamin D measured in subset to confirm expected changes with supplementation vs placebo.

INTERVENTION (# IN THE GROUP): 9,181

COMPARISON (# IN THE GROUP): 9,172

FOLLOW UP PERIOD: Median 5.3 years

RESULTS: There were no clinically significant changes between patients receiving vitamin D supplementation and those receiving placebo:

- Depression risk (Hazard Ratio [HR] 0.97; 95% CI, 0.87–1.1)
- Incident depression risk (HR 0.99; 95% CI, 0.87–1.1)
- Recurrent depression risk (HR 0.95; 95% CI, 0.76–1.2)

LIMITATIONS:

- PHQ-8 scores were self-reported.
- The study did not include all originally randomized parent trial participants.
- Eligibility requirements of the parent trial included only adults over 50 years old.

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The Kids Aren't Alright – How Modern Digital Media May Be Affecting the Minds of our Youth

Association of digital media use with subsequent symptoms of attention-deficit/hyperactivity disorder among adolescents

Ra CK, Cho J, Stone MD, et al. Association of Digital Media Use With Subsequent Symptoms of Attention-Deficit/Hyperactivity Disorder Among Adolescents. *JAMA*. 2018; 320(3):255–263. doi:10.1001/jama.2018.8931

KEY TAKEAWAY: High frequency use of digital media platforms is associated with increased odds of developing ADHD symptoms, with greater increase of symptom development when more platforms are used on a high frequency basis over time.

STUDY DESIGN: Prospective longitudinal cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Some literature, specifically a meta-analysis of studies on ADHD from 1987–2011, demonstrates a modest impact of traditional digital media (i.e. television, video games) in relation to the development of ADHD, which now affects an estimated 7% of youths. With increasing variability, accessibility, and faster than lightning speed of modern digital media, it remains to be determined how this affects the developing brains of the current adolescent population.

PATIENTS: Tenth grade students (age 15–16)

INTERVENTION: Self-reported high frequency digital media use

CONTROL: No high frequency use

OUTCOME: Development of 6 or more ADHD symptoms

METHODS (BRIEF DESCRIPTION):

- Out of 4,100 eligible students, 3,051 participants completed the full baseline survey
    - Excluded 198 participants with ADHD symptoms at baseline
- ADHD Current Symptoms Self-Report Form and frequency of activity on 14 media platforms were assessed at baseline and each follow up point
- Primary outcome was 6 or more of the 9 inattentive or 9 hyperactive/impulsive symptoms considered ADHD symptom-positive.
- High-frequency defined as "many times per day."
- Secondary analyses evaluated ADHD symptom prevalence as associated with high frequency media use across each of the 14 platforms.

INTERVENTION (# IN THE GROUP): Varied at each follow up point based on reported high-frequency media score

COMPARISON (# IN THE GROUP): Varied at each follow up point (414 to 495 students who reported 0 high-frequency use activities)

FOLLOW UP PERIOD: 6, 12, 18, and 24 months

RESULTS:

- There were significantly higher odds of ADHD symptom development with every additional high-frequency use digital platform (OR 1.1; 95% CI, 1.1–1.2) despite covariate adjustment (OR 1.1; 95% CI, 1.1–1.2)
- Secondary Outcomes – The prevalence of symptom development increased with high frequency use of each additional digital media platform:
    - Students with 7 high-frequency activities had a higher prevalence of ADHD symptoms compared to students with no high-frequency activities (9.5% vs 4.6%; difference of 4.9%; 95% CI, 2.5%–7.3%)
    - Students with 14 high-frequency activities had a higher prevalence of ADHD symptoms compared to students with no high-frequency activities (11% vs 4.6%; difference of 5.9%; 95% CI 2.6%–9.2%)
- The activity most associated with risk of ADHD symptoms was video chatting (adjusted OR 2.1; 95% CI 1.4–3.2)

LIMITATIONS:

- Unknown diagnostic history allows for the possibility of undiagnosed baseline ADHD.
- Self-reporting is unreliable for baseline exclusion of ADHD diagnosis and for media use.
- Other mental health disorders overlap symptoms with ADHD (i.e. depression and anxiety resulting in lack of focus/inattention, manic episodes in bipolar disorder often characterized by impulsivity).
- Uncontrolled environmental/parental and genetic influences.

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HIIT the Ground Running: High-Intensity Exercise and Quality of Life in Patients with Spondyloarthritis

High-intensity exercise improves fatigue, sleep, and mood in patients with axial spondyloarthritis

Sveaas SH, Dagfinrud H, Berg IJ, et al. High-Intensity Exercise Improves Fatigue, Sleep, and Mood in Patients With Axial Spondyloarthritis: Secondary Analysis of a Randomized Controlled Trial. *Phys Ther*. 2020; 100(8):1323–1332. doi:10.1093/ptj/pzaa086

KEY TAKEAWAY: High-intensity interval training improved fatigue, vitality, sleep, mood, and general health in patients with axial spondyloarthritis.
STUDY DESIGN: Secondary analysis of multisite, single blind randomized controlled trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Axial spondyloarthritis is a debilitating disease that affects thousands of people around the world. The mainstay of treatment, in conjunction with biologic agents, is physical therapy. High physical fitness has been shown to improve quality in the general population, and few patients with axial spondyloarthritis meet the national recommendations of physical activity.

PATIENTS: Patients with axial spondyloarthritis
INTERVENTION: High-intensity exercise regimen
CONTROL: No intervention
OUTCOME: Measured effects on fatigue, vitality, sleep, mood, and general health at 3 months follow up

METHODS (BRIEF DESCRIPTION):

- 100 patients with moderate to severe spondyloarthritis ages 23–69 patients from outpatient clinics at 4 Scandinavian hospitals.
- The intervention group consisted of strength and aerobic exercises.
  - Patients performed 40 minutes of cardiorespiratory exercise and 20 minutes of strength training three times weekly for a 3 month duration.
  - Patients were supervised by physical therapists and exercises were adjusted for pain.
- Outcomes were assessed by patient questionnaire measured prior to exercise and at 3-month follow up.
- A blinded assessor regulated the data collection.
- The Fatigue Severity Scale was used to assess fatigue.
- The vitality domain of the RAND 36-item Short form Health Survey was used to assess vitality.
- The Pittsburgh Sleep Quality Index was used to assess quality of sleep.
- The General Health Questionnaire-12 was used to assess mood.
- EuroQol was used to assess general health.

INTERVENTION (# IN THE GROUP): 50
COMPARISON (# IN THE GROUP): 50

FOLLOW UP PERIOD: 3 months and 12 months

RESULTS:

- At 3 months, patients saw reduced rates of fatigue (OR 0.41; 95% CI, 0.18–0.91) and poor sleep quality (OR 0.34; 95% CI, 0.13–0.92).
- Results showed moderate effect size in mean difference of fatigue (OR 0.58; 95% CI, 0.18–0.98) and vitality (OR 0.58; 95% CI, 0.18–0.98). Changes in mood, sleep quality, and perceived general health were statistically insignificant.
- At the 12-month follow up there was no statistically significant differences appreciated in fatigue, vitality, mood, sleep quality, and perceived general health compared to baseline, all exhibiting small effect sizes.

LIMITATIONS:

- Study power
- Selection bias, as patients recruited were likely highly-motivated given intensity of exercise program
- Subjects weren't blinded
- Outcomes are secondary outcomes of an original RCT

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Is Parenteral Anticoagulation the Only Choice for DVT in Cancer?

Apixaban an Effective Treatment for Venous Thromboembolism Associated with Cancer

Agnelli G, Becattini C, Meyer G, et al. Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer. *N Engl J Med*. 2020; 382(17):1599–1607. doi:10.1056/NEJMoa1915103

KEY TAKEAWAY: Apixaban is non-inferior to dalteparin in preventing recurrent venous thromboembolism (VTE) in patients with cancer.

STUDY DESIGN: Multinational, randomized, investigator-initiated, open-label, noninferiority trial with blinded central outcome adjudication

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Venous thromboembolism in patients with cancer is a common problem. Low molecular weight heparin has been the treatment of choice historically. Enteral factor Xa inhibitors have increasing evidence in this context but come with an increased risk of major bleeding.

PATIENTS: Adults with active cancer and newly diagnosed acute proximal deep vein thrombosis (DVT) or pulmonary embolism (PE)

INTERVENTION: Oral apixaban

CONTROL: Subcutaneous dalteparin

OUTCOME: Recurrent VTE

METHODS (BRIEF DESCRIPTION):

- Patients: Adults with cancer (excluding BCC, SCC, primary brain tumor, known intracerebral metastases, or acute leukemia) who presented with either symptomatic or incidental proximal lower limb DVT or PE
  - Qualifying patients had a new or recurring cancer diagnosis within the previous six months or started treatment within six months of randomization.
- Patients were randomized and assigned to receive either:
  - Apixaban: 10 mg BID x7 days, then 5 mg BID for 6 month total
  - Dalteparin: subcutaneously, 200 IU/kg x 1 month, followed by 150 IU/kg, total of 6 months
- Treatment was halted in cases with a platelet count <50,000/mm^3 or with conditions associated with risk of bleeding.
- Testing was performed if the patient had signs or symptoms that suggested VTE or bleeding.
- Recurrence of VTE was diagnosed via imaging.
- Major bleeding was defined as acute clinically overt bleeding with at least one of the following:
  - A drop in Hg by 2 g/dL
  - Requiring transfusion of 2 or more units of PRBCs
  - Bleeding at a critical site
  - Bleeding requiring surgical intervention
  - Fatal bleeding from initiation of treatment to 72 hours after the final dose.

INTERVENTION (# IN THE GROUP): 576

COMPARISON (# IN THE GROUP): 579

FOLLOW UP PERIOD: 1, 3, 6, and 7 months

RESULTS:

- Incidence of recurrent VTE for apixaban was no different than dalteparin (5.6% vs 7.9%; HR 0.63; 95% CI, 0.37–1.1)
- Use of apixaban was noninferior to dalteparin (*P*<.001 for noninferiority)
- Risk for major bleeding was similar between apixaban vs dalteparin (3.8% vs 4.0%; HR 0.82; 95% CI 0.40–2.5)

LIMITATIONS:

- Open label trial design
- GI bleeding endpoint was not pre-specified
- Not all cancer cases included
- Not adequately powered to evaluate for safety (bleeding)

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Starting Statin Therapy for Primary Prevention at Age 80: Are We Underutilizing Statins in 75+ Patients?

Association of statin use with all-cause and cardiovascular mortality in U.S. veterans 75 years and older

Orkaby AR, Driver JA, Ho YL, et al. Association of Statin Use With All-Cause and Cardiovascular Mortality in US Veterans 75 Years and Older. [published correction appears in *JAMA*. 2020 Oct 13;324(14):1468]. *JAMA*. 2020; 324(1):68–78. doi: 10.1001/jama.2020.7848.

KEY TAKEAWAY: Initiating statin therapy in patients over 75 years old without a history of atherosclerotic cardiovascular disease (ASCVD) significantly decreased all-cause and cardiovascular mortality.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: There have been few clinical trials studying statin therapy for primary prevention of ASCVD in patients over 75 years old. 2018 cholesterol guidelines consider prescribing statins in this population, but there is very limited evidence on the benefit of statins in this population.

PATIENTS: U.S. veterans 75 years and older

INTERVENTION: Initiation of any U.S. approved statin therapy

CONTROL: No statin use

OUTCOME: All-cause and cardiovascular mortality
Secondary Outcomes: Ischemic stroke, myocardial infarction (MI), revascularization with CABG or PCI, composite ASCVD events

METHODS (BRIEF DESCRIPTION):

- Cohort created using Veterans Health Administration (VHA) corporate data warehouse (CDW) to identify patients over 75 years old who utilized the VHA from 2002–2012 and for at least 2 years prior.
- Cohort inclusion criteria: No life limiting conditions, without ASCVD history, without a previous statin prescription (statin naïve)
- Cohort exclusion criteria: passed away within 150 days into cohort assignment
- Demographics: Mean age of 81 (75–107), 91.0%White, and 97.3% male
- Statin population assigned as prescriptions were started.
- Statins prescribed: Simvastatin (84.8%), lovastatin (11.0%), pravastatin (2.5%), fluvastatin (1.2%), remaining 0.5% were atorvastatin and rosuvastatin prescriptions.
- Outcomes (mortality, ASCVD events) and comorbidities were identified through CDW diagnosis codes and content management system (CMS) claims

INTERVENTION (# IN THE GROUP): 57,178

COMPARISON (# IN THE GROUP): 269,803

FOLLOW UP PERIOD: 2002 – 2012

RESULTS:

- Statin therapy compared to no statin use resulted in lower:
  - All-cause mortality incidents (weighted incidence rate difference [IRD] per 1,000: –20; 95% CI, –20 to –19)
  - Cardiovascular death incidents (weighted IRD per 1,000: –3.1; 95% CI, –3.6 to –2.6)
  - All-cause and cardiovascular mortality (propensity score overlap weighting all-cause mortality hazard ratio [HR], 0.75; 95% CI, 0.74–0.76)
  - Cardiovascular death (HR 0.80; 95% CI, 0.78–0.81)
  - Incidents of ASCVD (weighted IRD per 1,000: –4.1; 95% CI, –5.1 to –3.0)
  - Incidents of MI (weighted IRD per 1,000: 0.56; 95% CI, 0.13–0.98)
  - CABG surgery/PCI (weighted IRD per 1,000: –3.4; 95% CI, –4.1 to –2.6)
- Statin therapy did not affect incidents of ischemic stroke (weighted IRD per 1,000: 0.25; 95% CI, –0.26 to 0.76) or MI (HR 0.99; 95% CI, 0.97 to 1.03).

LIMITATIONS:

- Simvastatin, the primary statin used in this cohort is not reflective of current recommendations for statin intensity; this may underestimate results
- Small sample size of female patients and non-white patients
- Reliance on diagnostic codes and claims

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Lift and Go: Mesenteric Lift to Relieve Constipation in Traumatic Brain Injury Patients

Clinical Efficacy of Mesenteric Lift to Relieve Constipation in Traumatic Brain Injury Patients

Berry JAD, Ogunlade J, Kashyap S, et al. Clinical Efficacy of Mesenteric Lift to Relieve Constipation in Traumatic Brain Injury Patients [published online ahead of print, 2020 Aug 4]. *J Am Osteopath Assoc*. 2020;10.7556/jaoa.2020.094. doi:10.7556/jaoa.2020.094

KEY TAKEAWAY: The application of a mesenteric lift osteopathic manipulative medicine technique to patients with severe traumatic brain injury requiring intubation and intensive care unit placement may facilitate a return to normal bowel function within 24 hours.

STUDY DESIGN: Retrospective cohort medical record review

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Severe traumatic brain injury patients requiring intubation and intensive care placement experience multiple autonomic disturbances that interfere with normal gastrointestinal homeostasis and motility. A mesenteric lift osteopathic manipulative medicine technique is defined by *Foundations of Osteopathic Medicine (4th ed.)* as a technique in which the double layer of peritoneum that invests the intestines and its associated vascular, neural, and lymphatic structures is relieved of tension from the attachments to the posterior wall of the abdomen, which includes the root of the mesentery, hepatic, and splenic flexures and the ascending and descending colon.

PATIENTS: Those with severe traumatic brain injury requiring intubation and intensive care unit admission without bowel movement for 48 hours

INTERVENTION: Application of mesenteric lift technique in addition to prescription bowel regimen

CONTROL: Usual care

OUTCOME: Bowel movement documented within 24 hours

METHODS (BRIEF DESCRIPTION):

- All patients must have been admitted to the intensive care unit with:
  - Severe traumatic brain injury
  - Received bowel regimen consisting of daily doses of bisacodyl and docusate sodium
  - Received nastrogastric tube feeding within 24 hours of presentation
  - Received the same fluid management with 0.9% saline solution and maintenance fluid based on body weight
- Exclusion Criteria – Medical records indicated history of:
  - Blunt of penetrating trauma to the abdominal cavity
  - Injury to spine or spinal cord
  - Abdominal or pelvic surgery
  - Diabetes
- Patients were split between those that received mesenteric lift in addition to bowel regimen and those that only received the bowel regimen.
- The study was performed in an institution that included both osteopathic and allopathic neurosurgeons.
- Intervention patients receiving the mesenteric lift had the procedure performed by osteopathic neurosurgeons and residents under direct supervision.
- Control patients did not receive mesenteric lift when the allopathic neurosurgeons physicians were on call.

INTERVENTION (# IN THE GROUP): 35

COMPARISON (# IN THE GROUP): 44

FOLLOW UP PERIOD: 24 hours

RESULTS: More participants in the mesenteric lift group experienced a bowel movement in 24 hours compared to the usual care group (77% vs 36%; *P*=.01)

LIMITATIONS:

- Retrospective study design introducing selection bias and potential confounding variables secondary to limitations of medical record review .
- Incomplete medical records missing non-recorded bowl movements
- Small sample size
- Practice pattern variability between osteopathic and allopathic neurosurgeons

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