GEMs of the Week

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Week of July 25 - 29, 2022

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More than Five Years of Bisphosphonate Use Does Not Reduce Risk of Hip Fractures

Bisphosphonate treatment beyond 5 years and hip fracture risk in older women

Izano MA, Lo JC, Adams AL, et al. Bisphosphonate Treatment Beyond 5 Years and Hip Fracture Risk in Older Women. *JAMA Netw Open.* 2020; 3(12):e2025190. Published 2020 Dec 1. doi:10.1001/jamanetworkopen.2020.25190

KEY TAKEAWAY: Bisphosphonate treatment for >5 years in women 50–85 years old does not lower the risk for hip fracture.

STUDY DESIGN: Retrospective, observational, non-blinded cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Bisphosphonate therapy was introduced in the late 1990's. High-quality evidence is lacking for the continuation of this treatment to prevent bone fractures in women beyond the initial five years. There is conflicting evidence from low quality studies whether continuing this treatment offers additional protection regardless of risk factors. This study used data from a coordinated health system (Kaiser Permanente California) to correlate bisphosphonate use and risk of hip fracture for a cumulative total of five, seven, and 10 years of bisphosphonate therapy.

PATIENTS: Women 50-85 years old with at least five years of bisphosphonate treatment

INTERVENTION: Seven and ten years of bisphosphonate therapy

CONTROL: Five years of bisphosphonate therapy

OUTCOME: Hip fracture

METHODS (BRIEF DESCRIPTION):

- Electronic medical records were used to identify patients aged 50–85 years old, who had started bisphosphonate therapy between January 1997 and September 2009.
- Health plan coding data was used to identify a primary hospital discharge diagnosis of proximal femur fracture.
- Health plan pharmacy records were used to identify patient adherence to bisphosphonates.
- Inclusion criteria: Women aged 50–85 years old, taking bisphosphonates for five years, with greater than 60% adherence in pharmacy dispensed medication records (at least 60% of the five years since initiation were covered by days' supply of bisphosphonates in these records)
- Estimated socioeconomic status using surrogate markers from US Census block data.
- Used inverse probability weighting to adjust for complex time-varying confounders in comparing the between-group outcomes.

INTERVENTION (# IN THE GROUP):

- Seven years of treatment: 25,628
- Ten years of treatment: 25, 628

COMPARISON (# IN THE GROUP):

- Five years of treatment: 29,017

FOLLOW UP PERIOD: Five, seven, and ten years after bisphosphonate initiation

RESULTS:

- Bisphosphonate treatment for seven years did not decrease the incidence of hip fractures compared to five years of treatment (difference −2.2 per 1,000; 95% CI, −20 to 16 per 1,000 women).
- Bisphosphonate treatment for 10 years did not decrease the incidence of hip fractures compared to five years of treatment (difference 6.0 per 1,000; 95% CI, −9.9 to 22 per 1,000 women).

LIMITATIONS:

- Observational and non-randomized trial.
- Patients and treatment providers were not blinded.
- There was no control for allocating patients to interventions, which could have led to selection bias (provider discretion).
- Patient population may not be representative of national population based off ethnicity, BMI, smoking status, SES, or vitamin D deficiency.
- Only 39% of patients studied had diagnostic DEXA scans prior to starting treatment.
- High drop-out rate of 20% due to death, exclusion event, or end of Kaiser Permanente membership.
- Non-standard statistical methods due to time varying confounding.
- Included patients from before and after guidelines published by the National Osteoporosis Foundation Guide Committee were updated as well as availability of the fracture risk assessment tool (FRAX).

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Can Older Adults Exercise Their Way Out of Depression?

Effectiveness of Physical Exercise in Older Adults With Mild to Moderate Depression

Hidalgo JL, Sotos JR; DEP-EXERCISE Group. Effectiveness of Physical Exercise in Older Adults With Mild to Moderate Depression. *Ann Fam Med.* 2021; 19(4):302–309. doi:10.1370/afm.2670

KEY TAKEAWAY: In older adults, physical exercise for depression is no different than antidepressant medication after one month of treatment. However, antidepressant therapy was superior at months three and six despite a greater number of adverse effects.

STUDY DESIGN: Randomized clinical trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to high dropout rate)

BRIEF BACKGROUND INFORMATION: Depression is common, debilitating, and difficult to diagnose in the elderly. Antidepressants have unwanted side effects. If depression in the elderly could be treated with physical exercise, it would open new avenues to provide relief to many who suffer while decreasing potential for medication risk.

PATIENTS: Patients 65 years old and older with clinical depression

INTERVENTION: Physical Exercise

CONTROL: Antidepressant medication

OUTCOME: Decrease in depression symptoms

METHODS (BRIEF DESCRIPTION):

- 347 patients chosen from 10 different clinical sites. These patients were 65 years old and older who presented with the criteria of a clinically significant depressive episode. Depressive episodes could not be severe, and participants could not endorse suicidal ideation. The 10 different sites were all in the city of Albacete, in southern Spain.
- Patients were randomly assigned to the physical activity group or the antidepressant group.
- The physical activity group participated in a 1-hour exercise class twice a week that was run by an instructor. They participated in six months' worth of classes.
- The antidepressant group was assigned medication that the patient's physician deemed most appropriate.
- Participants were then scored using the Montgomery-Åsberg Depression Rating Scale (MADRS).
- A positive result was defined as a MADRS score of less than 10 points. This is indicative of an absence of depressive disorder.
- Follow up occurred at intervals of one month, three months, and six months.
- Due in part to a high dropout rate, results were analyzed with intent to treat analysis.

INTERVENTION (# IN THE GROUP): 158

COMPARISON (# IN THE GROUP): 155

FOLLOW UP PERIOD: Follow up at one, three, and six months

RESULTS:

- No significant difference in the absence of depression between the physical activity group and antidepressant group at one month (48% vs 54%; *P*<.01).
- More patients in the antidepressant group had an absence of depression compared to the physical activity group at three months (61% vs 46%; *P*<.01).
- More patients in the antidepressant group had an absence of depression compared to the physical activity group at six months (50% vs 33%; *P*<.01).
- The number of withdrawals or dropouts was significant in this study. At three and six months the physical activity group lost 39% of participants and 58% respectively, and the antidepressant group lost 23% and 40% respectively.
- Adverse side effects were greater in the antidepressant group vs the physical activity group (23% vs 9%; *P*=.007).

LIMITATIONS:

- High dropout rate. Out of 347 patients, only 159 completed the study.
- The nature of the trial precluded the option of blinding techniques.

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BNT162b2 Vaccine in Preventing Severe COVID-19 Outcomes in Adolescents

Effectiveness of BNT162b2 Vaccine against Critical Covid-19 in Adolescents

Olson SM, Newhams MM, Halasa NB, et al. Effectiveness of BNT162b2 Vaccine against Critical Covid-19 in Adolescents. *N Engl J Med.* 2022; 386(8):713–723. doi:10.1056/NEJMoa2117995

KEY TAKEAWAY: BNT162b2 vaccine in adolescents (ages 12–18 years old) prevents critical outcomes such as hospitalizations, ICU admissions, and life support therapies.
STUDY DESIGN: Case-control, test-negative design
LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: According to the CDC, although adults make up the majority of COVID-19 associated hospitalizations, there are a significant number of adolescent hospitalizations. COVID-19 associated hospitalization among adolescents has so far exceeded historical rates of hospitalizations for influenza related illnesses during comparable times of the year. Studies like this can help inform vaccination decisions and improve coverage.

PATIENTS: Pediatric patients between the ages of 12–18 years old
INTERVENTION: Patients hospitalized with COVID-19 illness
CONTROL: Two groups totaling, 777 controls hospitalized with non-COVID-19 illness (see methods below)
OUTCOME: Vaccine effectiveness determined by hospitalization secondary to COVID-19 infection, ICU admission, need of any life supporting interventions, death

METHODS (BRIEF DESCRIPTION):

- Surveillance period of the study May 30, 2021, to October 25, 2021. Patients were not followed afterwards.
- Odds of prior vaccination compared in laboratory-confirmed case patients and hospitalized controls without COVID-19 infection. This study evaluates the effectiveness of the vaccine to prevent the above outcomes using test-negative controls.
- Patients chosen aged 12–18 years old, admitted in one of 31 hospitals that are within the CDC-funded overcoming COVID-19 network.
- Patients needed to be hospitalized with the primary diagnosis of clinical presentation consistent with COVID-19 infection.
- Vaccination status was unvaccinated if there was no receipt of vaccination prior to onset of illness.
- Considered vaccinated if the most recent dose of their vaccine was given at least 14 days prior to onset of illness.
- Patients were considered partially vaccinated if they received only one dose of vaccine or if they received their second dose less than 14 days prior to onset of illness.
- Case group was 96% fully vaccinated.
- Controls: 57% unvaccinated, 36% fully vaccinated
  - Test-negative: 383 patients in first control group with symptoms consistent with COVID-19 infection but tested negative on PCR assay
  - Syndrome negative: 394 asymptomatic patients in the second control group

INTERVENTION (# IN THE GROUP): 445
COMPARISON (# IN THE GROUP): 777

FOLLOW UP PERIOD: Charts reviewed between May 30, 2021 to October 25, 2021

RESULTS:

- Effectiveness of BNT162b2 for hospitalization in both groups was 94% (95% CI, 90–96).
- BNT162b2 vaccination compared to no vaccination reduced:
  - ICU admissions by 98% (95% CI, 93–99)
  - Life support interventions by 98% (95% CI, 92–100)

LIMITATIONS:

- Vaccine effectiveness against specific variants was not studied.
- Hospitals in this trial were at urban centers, patients here may have more severe diseases.
- Low number of Black (24%) and Hispanic (25%) patients, disproportionately high number of patients from the southern United States, where COVID-19 infections were greater during the time of this study.
- The duration of protection also not fully studied.

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High-Intensity Exercise and Academic Achievement in Children

Exercise Intervention for Academic Achievement Among Children: A Randomized Controlled Trial

Takehara K, Togoobaatar G, Kikuchi A, et al. Exercise Intervention for Academic Achievement Among Children: A Randomized Controlled Trial. *Pediatrics.* 2021; 148(5):e2021052808. doi:10.1542/peds.2021-052808

KEY TAKEAWAY: HIIT-based exercise programs may improve academic achievement compared to normal physical education classes.
STUDY DESIGN: Randomized control trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The World Health Organization promotes physical activity for all children. Physical activity has been shown to improve academic achievement in school-aged children; however, large-scale trials have not been conducted. In this study, high intensity interval training (HIIT) based physical activity was compared to regular physical education classes to assess academic achievement.

PATIENTS: 4th grade students in selected Mongolian school districts
INTERVENTION: 10-minute HIIT-based exercise program
CONTROL: Normal physical education class
OUTCOME: Total mathematics and Mongolian language scores

METHODS (BRIEF DESCRIPTION):

- This study was conducted in 10 elementary schools in Mongolia over a 10-week period.
- The schools were separated into two categories, urban and mixed-residential areas.
- Enrolled children were in fourth grade, had written consent from parents/guardians, lived in selected Mongolian school districts, were born between February 2018 and December 2018 with the ability to speak, read, and understand Mongolian.
- The intervention group participated in a 10-minute HIIT-based exercise program, combined with music, which included three minutes each of jumps, squats, and steps, done twice weekly for a total of 10 to 25 minutes per session.
- The control group participated in normal physical education class including 10-minute warm-up and stretching, 30-minute team sport activities, and 5-minute cooldown.
- Academic achievement was assessed by total mathematics and Mongolian language scores on national examination, health outcomes, and cognitive function.

INTERVENTION (# IN THE GROUP): 1,069
COMPARISON (# IN THE GROUP): 1,032
FOLLOW UP PERIOD: 10 weeks

RESULTS:

- The HIIT-based exercise program improved academic achievement more than the normal physical education class.
  - Urban Area Mean Improvement: 8.4-point median improvement (95% CI, 6.1–10.7)
    - Mathematics: 6.2-point improvement (95% CI, 4.7–7.6)
    - Language: 2.3-point improvement (95% CI, 0.99–3.5)
  - Mixed-residential area mean improvement: 9.6-point median improvement (95% CI, 6.6–13)
    - Mathematics: 2.7-point improvement (95% CI, 6.6–13)
    - Language: 7.4-point improvement (95% CI, 5.8–9)

No significant differences between groups were found regarding lifestyle, mental health, and cognitive function.

LIMITATIONS:

- Measurement bias due to inability to blind the study.
- The measurement of the outcomes was conducted by individuals who knew the goal of the assignment.
- Bias due to missing outcome data due to transfers to schools outside the study area.
- The proportion of the missing outcome data was 7% in the intervention group and 12% in the control group.
- The study did not take participant's physical activity levels or program's exercise intensity into account.

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