GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of July 26 - 30, 2021

SPOTLIGHT: Different HPV Vaccine Types and Dose Schedules Provide Similar Prevention of HPV-related Disease

- Tai Chi Can Help Older Adults with Insomnia
- Strike Smart, Protect Your Head: Neurodegenerative Disease in Soccer Players
- Should You Check Labs After Treatment of Dermatophyte Infection with Terbinafine or Griseofulvin?

Different HPV Vaccine Types and Dose Schedules Provide Similar Prevention of HPV-related Disease

Comparison of Different Human Papillomavirus (HPV) Vaccine Types and Dose Schedules for Prevention of HPV-related Disease in Females and Males

Bergman H, Buckley BS, Villanueva G, et al. Comparison of different human papillomavirus (HPV) vaccine types and dose schedules for prevention of HPV-related disease in females and males. *Cochrane Database Syst Rev*. 2019; 2019(11):CD013479. Published 2019 Nov 22. doi:10.1002/14651858.CD013479

KEY TAKEAWAY: There is no significant difference in immunogenicity between valency or dosing schedules. However, there is a difference as it relates to dosing intervals.

STUDY DESIGN: Meta-analysis of 20 RCTs; N=31,940

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: HPV is responsible for more cases of STDs than any other pathogen. It is also responsible for up to 5% of cancers worldwide. As such ensuring that the most effective vaccine is given in the shortest time period is paramount.

PATIENTS: Unvaccinated males and females 9–26 years old

INTERVENTION: Schedule of 2 doses with varying valency

CONTROL: Schedule of 3 doses with varying valency

OUTCOME: Positive HPV titers

METHODS (BRIEF DESCRIPTION):

- A systematic review of international RCTs comparing two-dose and three-dose schedules of HPV vaccination
- Participants were limited to 9 to 26 years old unless they had HIV
- Studies comparing the length of time for dosing intervals of HPV vaccination were also included
- Intervention: Two-dose schedule along with different formulation of the HPV vaccine based on valency, an additional subset of HIV infected individuals without HPV vaccination history
- Comparison: Traditional three-dose schedule and HIV negative individuals

INTERVENTION (# IN THE GROUP): Not provided

COMPARISON (# IN THE GROUP): Not provided

FOLLOW UP PERIOD: 7 months – 5 years

RESULTS:

- Antibody responses were similar after five years for two-dose and three-dose HPV vaccine schedules (4 RCTs, moderate- to high-certainty evidence)
- Antibody responses were stronger with a longer interval (6 or 12 months) between the first two doses of HPV vaccine than a shorter interval (2 or 6 months) at up to three years of follow-up (4 RCTs, moderate- to high-certainty evidence).
- There was little to no difference in the incidence of the combined outcome of high-grade cervical epithelial neoplasia, adenocarcinoma in situ, or cervical cancer between the HPV vaccines (OR 1.0; 95% CI, 0.85 to 1.2).

LIMITATIONS:

- Need more time to determine if the vaccines are effective
- Highest risk populations, specifically in developing countries, are the least represented by the study
- Data not pooled or provided for most outcomes

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Tai Chi Can Help Older Adults with Insomnia

Effects of Tai Chi or Exercise on Sleep in Older Adults with Insomnia: A Randomized Clinical Trial

Siu PM, Yu AP, Tam BT, et al. Effects of Tai Chi or Exercise on Sleep in Older Adults with Insomnia: A Randomized Clinical Trial. *JAMA Netw Open*. 2021; 4(2):e2037199. Published 2021 Feb 1. doi:10.1001/jamanetworkopen.2020.37199

KEY TAKEAWAY: Tai chi is a comparable alternative to conventional exercise to improve nighttime awakenings in older adults. Tai chi is superior to conventional exercise in decreasing the use of sedative medications.
STUDY DESIGN: Randomized 3-arm parallel trial with blinded assessments
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: 20–40% of older adults suffer from insomnia but limited pharmaceutical interventions are available due to polypharmacy and physiological changes. Prior studies have found exercise to be an effective treatment for insomnia in older adults. Tai chi is a gentle exercise that does not interact with medications and is suitable for older adults.

PATIENTS: Adults ≥60 years old with chronic insomnia
INTERVENTION: Tai chi
CONTROL: Conventional exercise or passive control
OUTCOME: Nighttime awakenings
Secondary Outcomes: Need for medication, remission of insomnia, treatment response, insomnia severity

METHODS (BRIEF DESCRIPTION):

- Patients: Sedentary Chinese adults living in Hong Kong ≥60 years old with chronic insomnia
- Participants were randomized into blocks of tai chi, conventional exercise, or passive control
  - Both exercise groups met for 1 hour 3 times per week for 12 weeks
  - The tai chi training program was based on a Yang-style 24-form tai chi (most common type)
  - The conventional exercise program included brisk walking, stretching, deep breathing, and muscle strengthening
  - Passive control group did not do any exercises and only received phone call assessments
- Nighttime awakenings were measured with a wrist actigraph
- Insomnia remission was defined by no longer meeting DSM-V criteria for chronic insomnia
- Treatment response was defined by a decrease in Pittsburgh Sleep Quality Index (PSQI) score by at least 5 points
- Insomnia severity was assessed by Insomnia Severity Score (ISS)
- Assessments were conducted at baseline, week 12, and month 24

INTERVENTION (# IN THE GROUP): 105
COMPARISON (# IN THE GROUP):

- Control: 110
- Conventional Exercise: 105

FOLLOW UP PERIOD: 24 months

RESULTS:

- Participants in both exercise groups experienced less episodes of nighttime awakenings:
  - Tai chi group had *2.2 times fewer episodes* compared to control group (95% CI, –3.5 to –1.0)
  - Conventional group had *2.8 times fewer episodes* compared to control group (95% CI, –4.0 to –1.6)
  - Tai chi group showed *no statistically significant difference* when compared to conventional group (95% CI, –0.6 to 1.8)
- Participants in both exercise groups had decreased use of sedative-hypnotic medication compared to control:
  - Tai chi group patients had *4.0 times decreased use* of sedative hypotonic medications compared to control (95% CI, –5.5 to –2.5)
  - Conventional group patients had *2.1 times decreased use* of sedative medications compared to control (95% CI, –3.7 to –0.6)
  - Tai chi group had *1.4 times decreased use* of sedative medications compared to conventional group (95% CI, –3.6 to –0.2)

LIMITATIONS:

- Results may not be applicable to U.S. non-Asian patients.
- Outdoor venues may have contributed to improvement in sleep outcomes.
- 80% of participants in all groups were women.

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Strike Smart, Protect Your Head: Neurodegenerative Disease in Soccer Players

Neurodegenerative Disease Mortality among Former Professional Soccer Players

Mackay D, Russell ER, Stewart K, McLean J, Pell J, and Stewart W. Neurodegenerative Disease Mortality among Former Professional Soccer Players. *N Engl J Med*. 2019; 381(19):1801–8.

KEY TAKEAWAY: Playing professional soccer may be associated with higher mortality due to neurodegenerative disease after age 70.
STUDY DESIGN: Retrospective cohort study
LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Sports and exercise reduce mortality and decrease chronic cardiovascular disease. However, contact sports are associated with chronic traumatic brain disease. Mortality associated with repeated head injury in contact sports or chronic traumatic encephalopathy (CTE) has not been established.

PATIENTS: Adult Scottish males
INTERVENTION: Exposure to professional soccer
CONTROL: General population
OUTCOME: All-cause mortality from neurodegenerative disease
Secondary Outcomes: risk of neurodegenerative disease, cardiovascular risk, cancer, and medications

METHODS (BRIEF DESCRIPTION):

- Participants in the intervention group were professional soccer players ≥40 years old who were archived in the Scottish Soccer museum or played for individual clubs.
- The comparison group was matched with registry National Health Services Scotland by age, sex, year of birth, and degree of social deprivation (postal code-level database using community health index numbers)
- Diagnosis on death certificates and records of national prescribing information systems were evaluated for dementia.
- Codes for death with neurodegenerative disease: ICD-9 and ICD-10
- Data reviewed included records through 2016. The chart review was performed in 2018.
- Cox- proportional hazards regression used for time to death and mortality and sensitivity analysis (two sided $P<.05$)

INTERVENTION (# IN THE GROUP): 7,676 (1,180 deaths)
COMPARISON (# IN THE GROUP): 23,028 (3,908 deaths)

FOLLOW UP PERIOD: Median of 18 years

RESULTS:

- All-cause mortality was lower for soccer players compared to the general population (15% vs 17% respectively; Hazard Ratio [HR] 0.87; 95% CI, 0.80–0.93)
  - Former soccer player age at death: 68 ± 13 years
  - General population age at death: 65 ± 14 years
- Time dependent analysis revealed lower mortality for soccer players prior to being 70 years old but higher after, however cox proportional hazard assumption not met
- Former soccer players had a higher risk of neurodegenerative disease as a cause of death compared to the general population (2.9% vs 1.0%; HR 3.5; 95% CI, 2.7–4.6)
  - Former soccer players had a higher risk of neurodegenerative disease as the primary cause of death compared to controls (1.7% vs 0.5% respectively; subHR 3.5; 95% CI, 2.1–5.6)
- Neurodegenerative disease as a cause of death did not differ between goal keepers and outfielders (HR 0.73; 95% CI, 0.43–1.2).
- Dementia-related medications were prescribed less frequently to goal keepers than to outfielders (OR, 0.41; 95% CI, 0.19–0.89).

LIMITATIONS:

- Subjective: provider dependent reporting of diagnoses and cause of death
- Exposure to soccer may have varied (those in museum archives may have varied from individual clubs as far as aggressive or contact exposure)
- Reason for dementia medications not clearly defined

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Should You Check Labs After Treatment of Dermatophyte Infection with Terbinafine or Griseofulvin?

Utility of Laboratory Test Result Monitoring in Patients Taking Oral Terbinafine or Griseofulvin for Dermatophyte Infections

Stolmeier AD, Stratman HB, McIntee TJ, Stratman EJ. Utility of laboratory test result monitoring in patients taking oral terbinafine or griseofulvin for dermatophyte infections. *JAMA Dermatol*. 2018; 154(12):1409–1416.

KEY TAKEAWAY: In patients taking oral terbinafine or griseofulvin for dermatophyte infections, routine surveillance for ALT/AST elevation, anemia, neutropenia, or lymphopenia is unnecessary unless hepatic conditions exist prior to starting therapy.

STUDY DESIGN: Retrospective cohort

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Terbinafine and griseofulvin have been associated with hepatic and hematologic abnormalities. Therefore, routine baseline and interval laboratory testing has been recommended after initiating therapy. However, it is unclear if these lab tests are actually necessary as the rate of abnormalities is unknown.

PATIENTS: Those treated for dermatophyte infections (mean age 42)

INTERVENTION: Terbinafine or griseofulvin

CONTROL: N/A

OUTCOME: Rates of elevated ALT/AST, anemia, lymphopenia, and neutropenia

Secondary Outcomes: Rates of baseline abnormalities, frequency of results requiring additional testing or discontinuation, and monitoring practices

METHODS (BRIEF DESCRIPTION):

- Retrospective chart audits from 1/1/2006 – 12/31/2016
- Exclusion criteria: preexisting anemia, myelodysplastic syndrome, leukemia, cirrhosis, hepatitis, and alcohol abuse
- Baseline labs: Performed between 90 days prior to 7 days after initiating therapy
- Interval monitoring labs: Performed >7 days after initiation of therapy until completion of therapy
- Lab abnormalities graded utilizing the FDA Common Terminology Criteria for Adverse Events
  - Grade 1 = Mild: no intervention indicated
  - Grade 2 = Moderate: intervention indicated
  - Grade 3 = Severe: hospital intervention indicated
  - Grade 4 = Life threatening: urgent intervention indicated
  - Grade 5: Death related to adverse outcome
- Study interval resulted in 4,309 courses of terbinafine, 634 courses of griseofulvin microsize, and 159 courses of griseofulvin ultramicrosize.

INTERVENTION (# IN THE GROUP): 4,985 patients with 5,102 distinct medication courses

COMPARISON (# IN THE GROUP): N/A

FOLLOW UP PERIOD: 10 years

RESULTS:

- Patients taking terbinafine experienced:
  - Four cases (0.2%) of Grade 2 or higher ALT
  - One case (0.1%) of Grade 2 or higher AST
  - One case (0.1%) of Grade 2 or higher anemia
  - No cases of neutropenia
  - Five cases (0.7%) of Grade 2 or higher lymphopenia.
- Patients taking griseofulvin microsize experienced:
  - No change in ALT, AST or anemia
  - Three cases (0.4%) of Grade 2 or higher neutropenia
  - One case (1%) of Grade 2 or higher lymphopenia
- Patients taking griseofulvin ultramicrosize experienced:
  - No Grade 2 or higher abnormalities of ALT, AST, anemia, neutropenia or lymphopenia

Secondary Outcomes

- Combined, patients taking terbinafine or griseofulvin (microsize and ultramicrosize) experienced:
  - 0.23% had Grade 2 or higher LFT abnormalities
  - Only one patients experienced hepatotoxicity which resolved after discontinuation of medication
- To find one actionable abnormality, need to check:
  - 417 ALT
  - 455 AST
  - 2,297 hemoglobin counts
  - 997 neutrophil counts
  - 1,971 lymphocyte counts

LIMITATIONS:

- Primarily White population
- Cannot confirm medication taken properly or at all
- Substantial variability in timing and frequency of interval labs

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