GEMs of the Week

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GEMs
GOOD EVIDENCE MATTERS

FPIN
Family Physicians Inquiries Network

What's in this week's issue?

Week of March 22 - 26, 2021

SPOTLIGHT: Lower Childhood Socioeconomic Position Increases Risk of ACEs

Lower Childhood Socioeconomic Position Increases Risk of Adverse Childhood Experiences (ACEs)

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Relationship between childhood socioeconomic position and adverse childhood experiences (ACEs): a systematic review

Walsh D, McCartney G, Smith M, Armour G. Relationship between childhood socioeconomic position and adverse childhood experiences (ACEs): a systematic review. *J Epidemiol Community Health*. 2019; 73:1087–1093.

KEY TAKEAWAY: There is a strong relationship between socioeconomic position (SEP) and risk of experiencing adverse childhood experiences (ACEs) or maltreatment.

STUDY DESIGN: Systematic review of 35 observational studies (18 high quality, 5 medium quality, 12 low quality)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: An increasing number of exposure to ACEs (parental substance misuse, parental incarceration, and witnessing domestic violence) have a direct correlation with health harming behaviors such as committing domestic violence, abusing heroin/cocaine, binge drinking, and poor diet. However, the role of childhood SEP's influence on ACEs and adult life has not been well studied.

PATIENTS: Children of various socioeconomic positions (low parental income, minimal parental education, children living in disadvantaged neighborhoods)

INTERVENTION: Children of lower SEP

CONTROL: Relevant general population

OUTCOME: Effect of SEP on ACEs and maltreatment

METHODS (BRIEF DESCRIPTION):

- A literature search using the following key terms was conducted: "adverse childhood experiences," "socioeconomic status," and "maltreatment."
- Inclusion Criteria:
  - Described social position of parents/household in early years of childhood
  - Utilized several different measurements of adversity during childhood
  - The primary outcome of interest was childhood adverse event(s)
  - Relationship between social status and childhood adverse events could be measured statistically
- A modified version of the Hamilton Tool used 6 criteria to assess the quality of studies (low quality 0–4; medium quality 5; high quality 6–7):
  - Demonstrable representativeness
  - Individual or household exposure
  - Individual level measure of childhood adversity
  - Over adjustment for analysis
  - Sample size
  - External assessment or self-reported maltreatment

INTERVENTION (# IN THE GROUP): Varied by study (92 to >1,000,000 individuals)

COMPARISON (# IN THE GROUP): General population samples

FOLLOW UP PERIOD: Varied by study

RESULTS: The more disadvantaged the circumstance the more likely the child would develop ACEs compared to more privileged children.

- Approximately 10.8% of children in lower income groups experienced 4 or more ACEs compared to 1% of children in higher income groups
- Children living in the bottom fifth quintile for household income were 5.73 times more likely to develop 3 or more ACEs by age 8, 66% of children had 1 or more ACE, and 10% experienced 3 ACEs
- Low socioeconomic status a had relative risk of 2.11 (CI 1.16–3.84) of developing alcohol/drug dependence
- An increased prevalence of ACEs was noted in people who were not poor at birth but became poor by age of 15
  - This could be attributed to parental separation or death at a certain point in child's life
- In the US, low income women with financial problems experienced significantly more ACEs in all areas. Conversely higher level of maternal educational attainment and employment was associated with a lower risk of maltreatment.

LIMITATIONS:

- Wide variability in definitions of ACEs and maltreatment
- Articles published before 1998 were not included.
- Non-English papers were excluded.
- Only 6 of the 18 high quality studies were performed in the USA.
- No measurements of heterogeneity; lack of consistency in reporting and measuring ACEs

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Risk Factors Associated with Lengthened Symptomatic Mild Traumatic Brain Injury in Pediatric Sports Injuries

Risk Factors for Prolonged Symptoms of Mild Brain Injury: A Pediatric Sports Concussion Clinic Cohort

Fehr SD, Nelson LD, Scharer KR, et al. Risk Factors for Prolonged Symptoms of Mild Traumatic Brain Injury. *Clinical Journal of Sport Medicine*. 2019; 29(1):11-17.

KEY TAKEAWAY: Initial symptom severity, female sex, and self-reported loss of consciousness is related to prolonged duration of mild traumatic brain injury (mTBI) symptoms in pediatric patients.

STUDY DESIGN: Retrospective Cohort Study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Concussion or mTBI is a common problem seen in pediatric primary and specialty-sport clinics. Risk factors associated with prolonged recovery are not fully understood. Although it is known that the initial symptom severity score is predictive of prolonged recovery, females have been relatively underrepresented in sports-related concussions. Counseling patients and their families on the expected outcome of mTBI can be challenging without further elucidation of the risk factors associated with prolonged recovery.

PATIENTS: Pediatric patients with history of concussion, mTBI, or post-concussive syndrome

INTERVENTION: N/A

CONTROL: N/A

OUTCOME: Time to self-reported symptom recovery, predictors of prolonged recovery

METHODS (BRIEF DESCRIPTION):

- Included: all patients ages 10–18 years old seen in a sports concussion clinic from January 2010–May 2012 in Milwaukee, WI with a diagnosis of concussion, mTBI, or post-concussive syndrome.
- Excluded: complicated TBI, positive imaging, loss of consciousness >30 minutes, post-traumatic amnesia >24 hours
- Symptom severity defined as total Postconcussion Symptom Scale (PCSS) score at the first visit.
- Cox proportional hazards model used to calculate time to reach self-reported symptom recovery and evaluation of predictor variables.
- 109 cases censored as fully recovered prior to first visit.

INTERVENTION (# IN THE GROUP): 431 (540 in total clinic sample)

COMPARISON (# IN THE GROUP): N/A

FOLLOW UP PERIOD: N/A (retrospective chart review 2010–2012)

RESULTS: Patients presented 11 days (median) after injury and with 40 days (median) to symptom recovery (34 days in full clinic sample; N=540).

Univariate analysis demonstrated the following single predictors of prolonged recovery: female sex, positive loss of consciousness, higher symptom severity at first visit, and sport.

Cox regression analysis demonstrated 3 predictors in the final model associated with prolonged recovery:

- Female Sex (Hazard ratio [HR] 0.61)
- Higher initial symptom severity (HR 0.76)
- Positive loss of consciousness (HR 0.54)

No significant interactions were noted.

LIMITATIONS:

- Study occurred in a pediatric sports medicine clinic which may limit generalizability.
- Symptom duration and loss of consciousness based on self-report which may introduce bias.
- Retrospective nature of this study limits conclusions.

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Oseltamivir: Will You Feel Better Faster?

Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial

Butler CC, van der Velden AW, Bongard E, et al. Oseltamivir plus usual care versus usual care for influenza-like illness in primary care: an open-label, pragmatic, randomised controlled trial. *Lancet*. 2020; 395(10217):42–52.

KEY TAKEAWAY: Oseltamivir plus usual care for influenza-like illness decreases time to recovery compared to usual care alone.

STUDY DESIGN: Open-label, pragmatic randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded from STEP 2 given no placebo control)

BRIEF BACKGROUND INFORMATION: Oseltamivir is often used to treat confirmed or suspected influenza. However, oseltamivir may not be prescribed due to cost, concern for side effects, and lack of effectiveness.

PATIENTS: European patients >1 year of age with onset of influenza-like symptoms within prior 72 hours

INTERVENTION: Oseltamivir, twice daily for 5 days, dosed by weight

CONTROL: Usual care

OUTCOME: Patient-reported time to recovery

METHODS (BRIEF DESCRIPTION):

- Patients presented to primary care with a sudden onset of self-reported fever plus at least one respiratory symptom beginning within the last 72 hours during a seasonal influenza epidemic.
- Patients assigned to routine care or routine care plus oseltamivir, dosed by weight.
- Data: clinician-determined severity, length of symptoms, comorbidities, temperature, pulse, patient-reported severity of symptoms, and recommendations for usual care
- Oropharyngeal, nasal, and nasopharyngeal swabs were gathered to determine origin of respiratory pathogen, including influenza A and B, but results were not accessible to clinicians to not affect management.
- Patients recorded symptoms for 14 days and when they returned to baseline daily activities.

INTERVENTION (# IN THE GROUP): 1,533
COMPARISON (# IN THE GROUP): 1,526

FOLLOW UP PERIOD: Symptoms recorded for 14 days; telephoned at days 2–4, days 14–28, and after 28 days

RESULTS:

- The oseltamivir group had a shorter recovery time than the usual care group (5.7 days vs 6.7 days; mean difference, 1.0 day; 95% CI, 0.74 to 1.3)
- Patients ≥ 65 years of age with comorbidities and severe disease in the oseltamivir group had the greatest benefit of a shorter recovery time (mean difference, 3.2 days; 95% CI, 1.0 to 5.5)

LIMITATIONS:

- Clinicians determined severity of illness
- Symptoms subjective and reported by patients
- Term "usual care" is vague
- Benefit may be attributable to placebo effect given that the benefit of oseltamivir was similar for patients whether or not influenza test was positive

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Rate Control = Rhythm Control: Can It All Be So Simple?

Early rhythm-control therapy in patients with atrial fribrillation

Kirchhof P, Camm AJ, Goettee A, et al. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med*. 2020; 383(14):1305–1316.

KEY TAKEAWAY: Early rhythm-control in high-risk patients with newly diagnosed atrial fibrillation (AF) results in lower rates of cardiovascular mortality, stroke, and hospitalization for worsening heart failure and acute coronary syndrome versus rate-control alone.

STUDY DESIGN: RCT

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Current guidelines reserve the use of rhythm-control therapies for patients who remain symptomatic with AF despite adequate rate-control, as previous trials have failed to demonstrate a significant difference in outcomes between the two.

PATIENTS: Adults with cardiovascular comorbidities who were diagnosed with atrial fibrillation ≤12 months before enrollment

INTERVENTION: Early rhythm-control

CONTROL: Usual care

OUTCOME: Composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome; number of nights spent in the hospital per year

METHODS (BRIEF DESCRIPTION):

- Eligible patients: documented AF from contracted study sites throughout Europe; high risk for AF and receiving care screened for asymptomatic AF via ambulatory single-lead ECG
  - Inclusion criteria: >75 years old with a history of TIA or stroke OR two of the following criteria: >65 years old, female, heart failure, hypertension, diabetes mellitus, severe coronary artery disease, chronic kidney disease, left ventricular hypertrophy
  - Exclusion criteria: life expectancy <1 year, pregnant or potential to conceive, breastfeeding, drug abuse, prior AF ablation or surgery, previously failed amiodarone therapy, contraindication to rhythm therapy, severely stenotic or prosthetic MV, hepatic dysfunction requiring therapy, uncontrolled thyroid dysfunction, stage V renal dysfunction
- Randomized into early rhythm-control or usual care open-label, parallel groups:
  - Early rhythm-control group: antiarrhythmic drugs or AF ablation, rate-control therapy, and cardioversion for persistent atrial fibrillation
  - Usual care group: rate-control drugs alone, with rhythm-control therapy reserved for uncontrolled AF symptoms
- Baseline assessments/measures: medical history, clinical characteristics, therapy, and symptom status
  - Patients were re-evaluated at 1 and 2 years
- Outcome assessments were blinded

INTERVENTION (# IN THE GROUP): 1,395

COMPARISON (# IN THE GROUP): 1,394

FOLLOW UP PERIOD: Median of 5.1 years

RESULTS:

- Lower risk of composite death from cardiovascular disease in early rhythm-control vs usual care (3.9 per 100 person years vs 5 per 100 person years; HR 0.78; 95% CI, 0.66–0.92)
- No significant difference in days per year hospitalized in early rhythm-control vs usual care (5.8 ± 21.9 vs 5.1 ± 15.5; *P*=.23)

LIMITATIONS:

- Open trial design
- The most symptomatic patients were likely excluded
- Only collected detailed information on recurrent AF in the early rhythm-control group
- Much of the data relied on patient self-reporting
- None of the sites included were located in the United States

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A Better Outcome in Triple-Negative Breast Cancer

Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double blind, phase 3 trial
Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double blind, phase 3 trial. *Lancet*. 2020; 396: 1090–100.

KEY TAKEAWAY: The addition of neoadjuvant atezolizumab to sequential nab-paclitaxel and anthracycline-based chemotherapy protocol increases the pathologic complete response outcome in a statistically significant amount for early stage patients with triple-negative breast cancer.
STUDY DESIGN: Randomized, multicenter, multinational, double-blind, phase 3 trial
LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Triple-negative breast cancer has classically been the worst prognosis among breast cancers. This is due to the overamplification of human epidermal growth factor receptor 2 (HER2) and the complete lack of progesterone and estrogen receptors, which guide the treatment specific protocols in other breast cancers. Triple-negative breast cancer accounts for 10–20% of all early stage new breast cancer diagnoses. Historically, the 5-year survival rate has been around 70%.
PATIENTS: Patients with early stage triple-negative breast cancer (TNBC), staged I–III
INTERVENTION: Addition of neoadjuvant atezolizumab to nab-paclitaxel and anthracycline-based chemotherapy
CONTROL: Placebo + standard chemotherapy
OUTCOME: The pathologic complete response (eradication of invasive tumor for breast and lymph nodes) with the addition of neoadjuvant atezolizumab to chemotherapy protocol vs chemotherapy protocol alone

METHODS (BRIEF DESCRIPTION):

- Among the patients studied were women or men greater than or equal to age 18 years, stage cT2-T4, triple-negative breast cancer found on histology, no personal history of receiving therapy for TNBC or anthracycline or taxane therapy for any other type of cancer.
- The atezolizumab and chemotherapy group received intravenous atezolizumab every two weeks and nab-paclitaxel weekly for twelve weeks, then an eight week course of every two week atezolizumab, doxorubicin, and cyclophosphamide with filgrastim/pegfilgrastim support, concluded with breast surgery.
- The placebo plus chemotherapy group received 12 weeks of intravenous placebo combined with nab-paclitaxel once a week, followed by an 8 week course of intravenous placebo plus doxorubicin and cyclophosphamide every two weeks with filgrastim/pegfilgrastim, concluded with breast surgery.
- For both groups, radiotherapy was approached as clinically indicated.
- The outcomes were measured by complete pathologic response in the study group, control group, and then also reported in the PD-L1 (programmed cell death ligand 1) positive and negative groups.

INTERVENTION (# IN THE GROUP): 165
COMPARISON (# IN THE GROUP): 168

FOLLOW UP PERIOD: Median of 20–21 months

RESULTS:

- Pathologic complete response was achieved more in the intervention group compared to placebo (58% vs 41%; rate difference 17%; 95% CI, 6–27; *P*=.004)
- Pathologic complete response was achieved more for those patients PD-L1-positive in the intervention compared to placebo (69% vs 49%; rate difference 20%; 95% CI, 4–35; *P*=.021)

LIMITATIONS: This study was not powered for a long term response of overall survival or event-free survival.

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