GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of June 13 - 17, 2022

SPOTLIGHT: Psychotherapy and Pharmacotherapy are Comparable in Decreasing Depression Symptoms in Primary Care Setting

- Increased Risk of Adverse Neonatal Outcomes with Marijuana Exposure
- Increased Risk of Pregnancy-Related Hypertensive Disorders with One Elevated Blood Pressure over 130/80
- Specialized Back Pain Treatment on Healthcare Costs and Productivity
- COVID Vaccine Boosters: Which Regimen is Best?

Psychotherapy and Pharmacotherapy are Comparable in Decreasing Depression Symptoms in a Primary Care Setting

Psychologic Treatment of Depression Compared With Pharmacotherapy and Combined Treatment in Primary Care: A Network Meta-Analysis

Cuijpers P, Oud M, Karyotaki E, et al. Psychologic Treatment of Depression Compared With Pharmacotherapy and Combined Treatment in Primary Care: A Network Meta-Analysis. *Ann Fam Med*. 2021;19(3):262-270. doi:10.1370/afm.2676

KEY TAKEAWAY: In the primary care setting, pharmacotherapy and psychotherapy are similar in decreasing depressive symptoms, with combined therapy showing significant increase in benefit when compared to psychotherapy alone, but not when compared to pharmacotherapy alone.

STUDY DESIGN: Network meta-analysis of 58 RCTs (N=9,301)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Many studies have examined the effects of pharmacotherapy, psychotherapy, and combined therapy on depressive symptoms. These studies have shown that these interventions decrease symptoms of depression. However, there is limited information on the effect of these treatment strategies compared to each other in a primary care setting.

PATIENTS: Patients with depression

INTERVENTION: Pharmacological therapy, psychotherapy, or combined

CONTROL: Interventions compared to each other, wait list, and care as usual

OUTCOME: At least 50% improvement of depressive symptoms from baseline

METHODS (BRIEF DESCRIPTION):

- A comprehensive literature review using PubMed, PsycInfo, Embase, and Cochrane Library was conducted.
- Articles in English, Spanish, Dutch, and German were reviewed.
- Articles included were RCTs that contained data on:
  - Participants aged 18 years old or older
  - Participants that were recruited in the primary care setting
  - Participants that were diagnosed with depression as determined by diagnostic review or self-reported questionnaires
  - Comparison of psychologic treatment with pharmacotherapy, combined treatment, care as usual (no change in management), or waitlist (patient unable to initiate different modality during research period)
- Analysis did not focus on specific pharmacotherapy or psychotherapy modality.
- After duplicates were removed, 16,701 abstracts were examined, and 2,533 full text articles were reviewed.
- Of those reviewed, 58 RCTs were included in this meta-analysis.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW UP PERIOD: Due to wide range of follow up periods, data past six months was not analyzed.

RESULTS:

Treatment response was viewed as successful if there was a 50% decrease in depression symptoms.

- Psychotherapy, pharmacotherapy, and combined therapy were all successful when compared to the "care as usual" group.
  - Psychotherapy: RR 1.6; 95% CI, 1.4–1.8
  - Pharmacotherapy: RR 1.7; 95% CI, 1.4–2.0
  - Combination therapy: RR 2.2; 95% CI, 1.6–3.0
- Psychotherapy, pharmacotherapy, and combined therapy were all effective when compared to the "wait list" group.
  - Psychotherapy: RR 2.4; 95% CI, 1.6–3.5
  - Pharmacotherapy: RR 2.4; 95% CI, 1.6–3.7
  - Combination therapy: RR 3.2; 95% CI, 1.9–5.2
- No significant difference was found between psychotherapy and pharmacotherapy alone for response (RR 1.0; 95% CI, 0.88–1.2).
- Combined therapy was found to be more effective than psychotherapy alone (RR 1.4; 95% CI, 1.0–1.8).
- No significant difference was found between combination therapy and pharmacotherapy alone (RR 1.3; 95% CI, 0.98–1.7).

LIMITATIONS:

- Low power of studies that included combined therapy when compared to pharmacotherapy and psychotherapy alone. May understate the effects of combined therapy in primary care.
- Difficult to assess the effects of individual psychotherapy modalities as no evaluation of individual modalities was included.
- Number of patients in each treatment group

was not reported.

- Difficult to assess the effects of individual medications as no evaluation of individual medication treatment was included.
- Data only analyzed to six months.

Jacob Parmley, DO
University of Wyoming FMR
Casper, WY

Increased Risk of Adverse Neonatal Outcomes with Marijuana Exposure

Birth Outcomes of Neonates Exposed to Marijuana in Utero: A Systematic Review and Meta-analysis

Marchand G, Masoud AT, Govindan M, et al. Birth Outcomes of Neonates Exposed to Marijuana in Utero: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2022; 5(1):e2145653. Published 2022 Jan 4. doi:10.1001/jamanetworkopen.2021.45653

KEY TAKEAWAY: Exposure to marijuana in utero increases risk of adverse neonatal outcomes such as a birth weight <2,500 g, small for gestational age (SGA), preterm delivery, and neonatal intensive care unit (NICU) admission.

STUDY DESIGN: Systematic review and meta-analysis of 16 cohort studies (N=59138)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Previous studies have reported inconsistent neonatal adverse effects with marijuana use in pregnancy. Marijuana use in pregnancy has been underreported with some cultural belief that it is safe to use in pregnancy. Fetal cannabinoid receptors develop in the 2nd trimester and THC, the main psychoactive component, crosses the placenta freely. Given recent state legalization of marijuana, its use is expected to increase.

PATIENTS: Pregnant women

INTERVENTION: Marijuana exposure

CONTROL: No marijuana exposure

OUTCOME: Birth weight, small for gestational age, preterm delivery, birth weight, NICU admission rate, gestational age at delivery, APGAR, infant head circumference, infant length

METHODS (BRIEF DESCRIPTION):

- Literature search and review of all intervention and observational studies up until October 16, 2021 that included pregnant women exposed and not exposed to marijuana with the above outcomes.
- Outcomes were determined prior to initiating data collection.
  - Birth weight <2,500 g, small for gestational age (birth weight <5th percentile), preterm delivery rate (<37 weeks), birth weight, NICU admission rate, gestational age at delivery, 1 min APGAR, 5 min APGAR, 5 min APGAR <7, infant head circumference, and infant length
- Literature search and NIH quality assessment was performed largely by two authors with a 3rd author present for any disputes.

INTERVENTION (# IN THE GROUP): 6,585

COMPARISON (# IN THE GROUP): 52,553

FOLLOW UP PERIOD: Variable, some studies validated marijuana positivity based on UDS at delivery or simply by self-reporting. All studies were retrospective, with some lasting up to four years.

RESULTS:

- Maternal marijuana exposure during pregnancy had significantly increased risk of the following neonatal outcomes:
  - Birth weight <2,500 g (RR 2.1; 95% CI, 1.3–3.4)
  - Small for gestational age (RR 1.6; 95% CI, 1.4–1.8)
  - Pre-term delivery (RR 1.3; 95% CI, 1.2–1.4)
  - NICU admission (RR 1.4; 95% CI, 1.2–1.6)

LIMITATIONS:

- Some studies relied heavily on patient honesty about their marijuana use/exposure.
- Most studies didn't differentiate the scope of marijuana use (heavy/daily use vs one time vs first trimester only).
- Possibility of confounding factors in some of the studies, including socioeconomic status, prenatal care, or alcohol use.
- All 16 studies were cohort studies and thus may have retrospective bias.

Chelsea Crouch, DO
Marquette Family Medicine Residency Program
Marquette, MI

Increased Risk of Pregnancy-Related Hypertensive Disorders with One Elevated Blood Pressure over 130/80

Pregnancy Outcomes Associated With A Single Elevated Blood Pressure Before 20 Weeks of Gestation

Duffy JY, Getahun D, Chen Q, Fong A. Pregnancy Outcomes Associated With a Single Elevated Blood Pressure Before 20 Weeks of Gestation. *Obstet Gynecol*. 2021; 138(1):42–50. doi:10.1097/AOG.0000000000004422

KEY TAKEAWAY: A single elevated blood pressure over 130/80 before 20 weeks gestation increases the risk of developing pregnancy-related hypertensive disorders and adverse neonatal outcomes.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: In 2017, the American College of Cardiology and the American Heart Association lowered the diagnostic criteria for hypertension from 140/90 to 130/80. Few studies have examined if a single elevated blood pressure, using the 130/80 cut off, is associated with adverse pregnancy outcomes.

PATIENTS: Pregnant women

INTERVENTION: A single elevated blood pressure above 130 systolic and/or 80 diastolic

CONTROL: Normotension

OUTCOME: Hypertensive disorders of pregnancy

Secondary Outcomes: Maternal outcomes, delivery-related outcomes, neonatal outcomes.

METHODS (BRIEF DESCRIPTION):

- Electronic medical records for 303,689 pregnant women who had a live birth at a Kaiser Permanente Southern CA hospital during the study period were assessed.
- Exclusion criteria included known diagnosis of chronic hypertension using the 130/80 cutoff, <18 years old, multiple gestation, and less than two antenatal visits before 20 weeks gestation.
- Patients were divided into a normotensive group vs a single elevated blood pressure group based on any outpatient visit before 20 weeks gestation.
- Average patient age was 30 years old in both groups.
  - Other patient demographics including race, ethnicity, and parity were similar between the two groups.
- Primary and secondary outcomes were based on ICD-9 and ICD-10 diagnosis codes from outpatient and inpatient records.
- Maternal demographics, comorbidity and antepartum characteristics were compared using X^2 and *t*-tests, then standardized difference was calculated for each parameter.

INTERVENTION (# IN THE GROUP): 70,990

COMPARISON (# IN THE GROUP): 232,699

FOLLOW UP PERIOD: Through the end of pregnancy

RESULTS:

Primary Outcome –

- Women with a single elevated blood pressure before 20 weeks gestation were more than twice as likely to develop a hypertensive disease of pregnancy (11% vs 4.5%; adjusted OR 2.1; 95% CI, 2–2.1).

Secondary Outcome –

- The single elevated blood pressure group had higher rates of:
  - Gestational diabetes (adjusted OR 1.2; 95% CI, 1.1–1.2)
  - Placental abruption (adjusted OR 1.2; 95% CI, 1.1–1.3)
  - Stroke (adjusted OR 1.2; 95% CI, 1.1–1.4)
  - Postpartum hemorrhage (adjusted OR 1.0; 95% CI, 1.0–1.1)
  - Preterm delivery before 34 weeks (adjusted OR 1.3; 95% CI, 1.2–1.4)
  - Preterm delivery before 37 weeks (adjusted OR 1.2; 95% CI, 1.2–1.3)
  - Small for gestational age neonates (adjusted OR 1.1; 95% CI, 1.0–1.1)
  - Neonatal jaundice (adjusted OR 1.1; 95% CI 1–1.1)
  - Five-minute APGAR score of less than 7 (adjusted OR 1.2; 95% CI 1.1–1.3)
- Cesarean section delivery rates were similar between both groups.

LIMITATIONS:

- Approximately 10% of the deliveries during the study period were excluded due to the strict exclusion criteria of removing patients with less than two antenatal visits.
- Though data for patient's prescribed aspirin was obtained, it did not capture over-the-counter aspirin use or patient compliance with aspirin.

Georgia L. M. McCrary, DO
Camp Lejeune FMR
Camp Lejeune, NC

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Navy Medical Department, the Navy at large, or the Department of Defense.

Specialized Back Pain Treatment on Healthcare Costs and Productivity

The impact of specialized treatment of low back pain on health care costs and productivity in a nationwide cohort: A non-randomized cohort prospective study

Solumsmoen S, Poulsen G, Kjellberg J, Melbye M, Munch TN. The impact of specialised treatment of low back pain on health care costs and productivity in a nationwide cohort. *EClinicalMedicine.* 2021; 43:101247. Published 2021 Dec 24. doi:10.1016/j.eclinm.2021.101247

KEY TAKEAWAY: Specialized back treatment increases healthcare costs and reduces patient productivity before and after intervention.

STUDY DESIGN: Five-year, non-randomized prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Low back pain (LBP) is a growing cause of increased healthcare costs, decreased workforce productivity, and decreased quality of life worldwide. There has been a 54% increase in disability due to LBP in the past three decades.

PATIENTS: Danish patients with LBP who have not previously undergone spine surgery

INTERVENTION: Specialized surgical treatment or conservative treatment

CONTROL: Background controls

OUTCOME: Healthcare costs, productivity loss before and after intervention, impact of multiple surgeries, caregiver productivity loss

METHODS (BRIEF DESCRIPTION):

- Two cohorts:
  - Patients who underwent surgical treatment
  - Patients who continued conservative treatment
- Relevant ICD classification was used to identify relevant spine disease, however patients with congenital spinal malformation were excluded.
- Ten random controls (no treatment) were selected for each patient that underwent either treatment.
- The yearly healthcare costs and productivity loss were estimated for each year for five years, and then compared to two years before the index year.

INTERVENTION (# IN THE GROUP):

- 56,695 (Surgical management)
- 72,915 (Conservative management)

COMPARISON (# IN THE GROUP):

- 566,940 (Surgical background controls)
- 729,150 (Conservative background controls)

FOLLOW UP PERIOD: Five years

RESULTS:

- Surgical treatment increased direct healthcare costs by 44% (€2,378) at 2-years post-surgery; €5,364 compared to matched background controls of €2,986, and by 38% (€2,066) at 5-years post-surgery; €5,253 compared to matched background controls of €3,187.
- Five years post-surgery, the number of weeks on sick leave/disability pension increased by 71% (15/9 weeks) vs 8% (7/5 weeks) among background controls.
- Conservative treatment increased direct healthcare costs by 40% (€1,843) at 2-years post-intervention; €4,515 compared to matched background controls of €2,672, and 34% (€1,513) at 5-years post-intervention; €4,359 compared to matched background controls of €2,846.
- Five years after conservative management, the number of weeks on sick leave/disability pension increased by 79% (15/2 weeks) vs 16% (7/5 weeks) among background controls.
- Surgical and conservative management increased the number of weeks on sick leave/disability pension for patients' spouses at 5-year follow up compared to matched background controls (surgical; 7/1 weeks vs 5/8 weeks and conservative; 8/1 weeks vs 5/7 weeks).

LIMITATIONS:

- Since this is an observational study, true causality cannot be determined.
- Data was collected from one country (Denmark), which may limit the applicability.
- This study did not account for confounding variables, such as participants weight and comorbidities.

Dauda Rogers, MD
University of Arkansas Medical Sciences FMRP
Magnolia, AR

COVID Vaccine Boosters: Which Regimen is Best?

Immunogenicity and Reactogenicity of Vaccine Boosters after Ad26.COV2.S Priming

Sablerolles RSG, Rietdijk WJR, Goorhuis A, et al. Immunogenicity and Reactogenicity of Vaccine Boosters after Ad26.COV2.S Priming. *N Engl J Med*. 2022;386(10):951-963. doi:10.1056/NEJMoa 2116747

KEY TAKEAWAY: Compared to a single dose of Ad26.COV2.S (J&J vaccine), any SARS-CoV-2 booster vaccine, given three months after the priming dose, demonstrated increases in antibody levels, neutralizing antibody levels, and T-cell responses.

STUDY DESIGN: Single-blinded, multicenter, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: There has been much confusion over SARS-CoV-2 booster vaccines in individuals who initially had a single J&J vaccine. Therefore, an in-depth comparison regarding the efficacy of various booster regimens is needed.

PATIENTS: Healthcare workers 18–65 years old

INTERVENTION: Booster with another J&J vaccine, one BNT162b2 (Pfizer-BioNTech), or mRNA-1273 (Moderna)

CONTROL: No booster

OUTCOME: S-specific binding antibody levels

Secondary Outcomes: Levels of neutralizing antibodies, S-specific T-cell responses, and possible reactions after booster

METHODS (BRIEF DESCRIPTION):

- Participants were generally healthy, without comorbidities, history of COVID-19 infection, or immunocompromised status.
- All participants received a dose of J&J vaccine, then three months later, were randomly assigned 1:1:1:1 to receive no booster, J&J booster, Pfizer booster, or Moderna booster.
- Two visits, day 0, when they got their booster or no booster and had blood taken for measurements, and day 28, where another blood sample was taken.
- Each group, in each of the measured results, were compared to baseline levels in a median factor change in log-transformed values.
- All measured results were plotted via linear regression for the association between binding antibody levels and neutralizing antibody levels as well as between binding antibody levels and T-cell responses.
- Note: Results were presented as effect size (beta-coefficient). The higher the absolute value of the beta-co-efficient, the stronger the effect (for example, a beta-coefficient of -0.3 has less of an effect compared to +0.6).

INTERVENTION (# IN THE GROUP):

- J&J: 106
- Moderna: 112
- Pfizer: 111

COMPARISON (# IN THE GROUP): 105

FOLLOW UP PERIOD: 28 days

RESULTS: In all who received boosters, there were higher levels of S-specific binding antibodies, neutralizing antibodies, and T-cell responses.

- Increase in binding antibody levels:
  - J&J: Authors calculate this effect size to be a 3.3-fold increase in binding antibody levels compared to baseline (Beta 0.64; 98.3% CI, 0.41–0.81).
  - Pfizer: Effect size correlates to a 21-fold increase in binding antibody levels compared to baseline (Beta 0.73; 98.3% CI, 0.57–0.90).
  - Moderna: Effect size correlates to a 42-fold increase in binding antibody levels compared to baseline (Beta 0.94; 98.3% CI, 0.85–1.1).
- Increase in neutralizing antibody levels:
  - J&J: Effect size correlates to a 4.8-fold increase in neutralizing antibody levels compared to baseline (Beta 0.60; 95% CI, 0.35–0.75).
  - Pfizer: Effect size correlates to a 24-fold increase in neutralizing antibody levels compared to baseline (Beta 0.61; 95% CI, 0.54–0.70).
  - Moderna: Effect size correlates to a 41-fold increase in binding antibody levels compared to baseline (Beta 0.66; 95% CI, 0.60–0.76).
- Appropriate T-cell responses after boosting:
  - J&J: 73%
  - Pfizer: 92%
  - Moderna: 92%
- Vaccine related symptoms:
  - Most resolved within 48 hours and were all mild.
- Moderna was associated with more reactions.

LIMITATIONS:

- Participants had almost no comorbidities.
- Optimal booster interval unknown. Three months was randomly chosen.

- Antibody levels and T-cell responses were measured 28 days after booster. Optimal measurement time is unknown.
- Study only reviewed disease-oriented outcomes and not patient-oriented outcomes.

Patrick Correa, DO
Ocean University Medical Center FMR
Brick, NJ