GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Monthly Extended-Release Buprenorphine Injections Can Improve Opioid Use Abstinence

Monthly Extended-Release Buprenorphine Injections Can Improve Opioid Use Abstinence

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Efficacy and Safety of a Monthly Buprenorphine Depot Injection for Opioid Use Disorder: A Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase 3 Trial

Haight BR, Learned SM, Laffont CM, et al. Efficacy and safety of a monthly buprenorphine depot injection for opioid use disorder: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet.* 2019; 393(10173):778-790. doi:10.1016/S0140-6736(18)32259-1

KEY TAKEAWAY: Monthly dosing of buprenorphine depot injections lead to increased rates of abstinence and satisfaction compared to placebo.

STUDY DESIGN: Multicenter, randomized, double blind, placebo-controlled phase 3 trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Opioid use disorder (OUD) is a worldwide epidemic requiring a multimodal approach towards prevention and management. Medication-assisted treatment (MAT) that requires daily administration poses several risks and limitations. This study evaluates the efficacy and safety of a monthly buprenorphine depot injection.

PATIENTS: Adults with moderate or severe opioid use disorder

INTERVENTION: Monthly buprenorphine + counseling

CONTROL: Volume-matched placebo + counseling

OUTCOME: Abstinence from opioid use

Secondary Outcome: Treatment success, defined as ≥80% opioid abstinence during weeks 5–24; satisfaction

METHODS (BRIEF DESCRIPTION):

- Adults 18–65 years old (mean 39 years old) with moderate or severe opioid use disorder at 36 United States treatment centers.
- Exclusion criteria: MAT for OUD in preceding 3 months; moderate to severe alcohol use disorder (as well as cocaine and cannabis use disorders, if positive on urine drug screen); chronic opioid therapy for any diagnosis other than OUD.
- All participants received up to two weeks of buprenorphine/naloxone sublingual film in an open label run-in phase.
- Randomization to either:
  - Six monthly doses of BUP-XR 300 mg
  - Two monthly doses of BUP-XR 300 mg, followed by four doses of BUP-XR 100 mg
  - Volume-matched placebo
- Urine drug screen, self-reported drug use, COWS, SOWS, opioid craving VAS, safety assessments and pharmacokinetic analysis were collected weekly.
- Primary outcome measured by percentage of negative urine samples and self-reported opioid use from weeks 5–24.
- Satisfaction was measured by the Medication Satisfaction Questionnaire.

INTERVENTION (# IN THE GROUP):

- BUP-XR 300 mg: 201
- BUP-XR 300 mg then 100 mg: 203

COMPARISON (# IN THE GROUP): 100

FOLLOW UP PERIOD: 29 weeks

RESULTS:

Primary Outcome –

- The monthly buprenorphine groups (300 mg and 300 mg then 100 mg) had higher abstinence rates than the placebo group (41% vs 43% vs 5%, respectively; *P*<.0001).

Secondary Outcomes –

- The monthly buprenorphine groups (300 mg and 300 mg then 100 mg) had higher treatment success than the placebo group (29% vs 28% vs 2%, respectively; *P*<.0001).
- The monthly buprenorphine groups (300 mg and 300 mg then 100 mg) had higher satisfaction than the placebo group (88% vs 88% vs 46%, respectively; *P*<.0001).

LIMITATIONS:

- High number of participants discontinued.
- Study design not conducive to including controlled non-inferiority against transmucosal buprenorphine.
- Primarily male (66%) and white (71%).

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Our Hearts Tell Us TAILORed Therapy is Not Always Superior

Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial

Pereira NL, Farkouh ME, So D, et al. Effect of genotype-guided oral p2y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention. *JAMA*. 2020; 324(8):761.

KEY TAKEAWAY: Genotype-guided selection of an oral P2Y12 inhibitor compared with conventional clopidogrel therapy did not affect outcomes at 12 months.

STUDY DESIGN: Open label randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients who undergo percutaneous coronary intervention (PCI) with stent placement are typically placed on an oral P2Y12 inhibitor, most commonly clopidogrel, to prevent ischemic events. Some patients possess a CYP2C19 genotype (CYP2C19 loss-of-function [LOF] carriers) and are unable to convert clopidogrel to its active metabolite, placing them at increased risk of ischemic events. It is unknown if routine genotype-guided selection of oral P2Y12 inhibitors would improve outcomes.

PATIENTS: Adults with acute coronary syndrome (ACS) or stable coronary artery disease (CAD) who underwent PCI

INTERVENTION: Genotype-guided P2Y12 inhibitor selection

CONTROL: Conventional therapy

OUTCOME: Composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, severe recurrent ischemia

Secondary Outcomes: Major or minor bleeding

METHODS (BRIEF DESCRIPTION):

- Inclusion Criteria: ≥18 years old (median 62; range 21–95), treated with PCI for ACS or stable CAD, plan to complete 12 months of dual antiplatelet therapy (DAPT).
- Exclusion Criteria: Unable to receive 12 months of DAPT, known CYP2C19 genotype prior to randomization, failure of Index PCI, planned revascularization within 30 days of PCI.
- Randomized 1:1 to:
  - Genotype-guided selection group divided into two categories:
    - Participants *with* CYP2C19 LOF alleles received ticagrelor 90 mg orally (po) twice daily (bid) and aspirin (ASA) 81 mg daily for 12 months. If ticagelor was not tolerated patients received either prasugrel 10 mg po daily or clopiogrel 150 mg po daily for 12 months.
    - Participants *without* LOF alleles received clopidogrel 75 mg po and ASA 81 mg po daily for 12 months.
  - Conventional therapy (control group) received clopidogrel 75 mg po daily and ASA 81 mg po daily for 12 months. LOF status was determined at conclusion of study and those with LOF alleles compared to the LOF allele participants in the genotype guided group.

INTERVENTION (# IN THE GROUP): 903

COMPARISON (# IN THE GROUP): 946

FOLLOW UP PERIOD: 12 months

RESULTS: The genotype-guided selection group did not differ from the conventional therapy group in any of the measured outcomes.

- Composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, severe recurrent ischemia (HR 0.66; 95% CI, 0.43–1.02)
- Myocardial infarction (HR 0.82; 95% CI, 0.37–1.8)
- Major bleeding (HR 1.1; 95% CI, 0.45–2.4)
- Cardiovascular death (HR 0.49; 95% CI, 0.15–1.6)
- Stent thrombosis (HR 0.25; 95% CI, 0.05–1.2)

LIMITATIONS:

- The trial was underpowered to detect an effect size less than the 50% relative risk reduction.
- Insurance coverage of P2Y12 inhibitors led to some patients not receiving the specified antiplatelet therapy.
- The trial was not double-blinded.
- Potential benefit of genotype-guided therapy seen in the first three months after PCI was not addressed.
- Only 124 (2%) of participants were African American.

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Augmentin vs Fluoroquinolone + Metronidazole for Treatment of Outpatient Diverticulitis

Comparative Effectiveness and Harms of Antibiotics for Outpatient Diverticulitis: Two Nationwide Cohort Studies

Gaber CE, Kinlaw AC, Edwards JK, et al. Comparative Effectiveness and Harms of Antibiotics for Outpatient Diverticulitis: Two Nationwide Cohort Studies. *Ann Intern Med*. 2021; 174(6):737–746.

KEY TAKEAWAY: Outpatient treatment of diverticulitis with amoxicillin-clavulanate is as effective as treatment with metronidazole-with-fluoroquinolone and reduces the risk of harm associated with the use of fluoroquinolones.

STUDY DESIGN: Active-comparator, new-user retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Acute diverticulitis is a common inflammatory condition affecting the colon that may benefit from early outpatient treatment with antibiotics. Harms associated with fluoroquinolone use have led the U.S. Food and Drug Administration to advise that this class of antibiotic only be used when no alternative treatment options are available. To date there is uncertainty surrounding the comparative effectiveness of the two most common antibiotic regimens: metronidazole-with-fluoroquinolone and amoxicillin-clavulanate alone.

PATIENTS: Adults with their first occurrence of diverticulitis diagnosed in an outpatient setting

INTERVENTION: Treatment with amoxicillin-clavulanate

CONTROL: Treatment with metronidazole-with-fluoroquinolone

OUTCOME: Diverticulitis-related inpatient admission, urgent surgery, and *Clostridioides difficile* infection (CDI) within one year of diagnosis

Secondary Outcome: Elective surgery within three years of diagnosis

METHODS (BRIEF DESCRIPTION):

- Two separate cohort studies were conducted on two separate data sources: IBM MarketScan Commercial Claims and Encounters Database and a random sample of 20% of Medicare claims with Parts A, B, and D coverage from 2007–2015.
- Eligible patients were identified by their first occurrence of an outpatient diagnostic code for diverticulitis.
    - Exclusion criteria included any prior diagnostic code related to diverticulitis, percutaneous drain, colectomy, immunosuppression, immunocompromised state, or patients who filled a prescription for one of the study antibiotics within the prior six months.
- Outcome follow-up began at 14 days after the diagnosis date, and ended with outcome occurrence, death, disenrollment from the database, or the end of the study period.

INTERVENTION (# IN THE GROUP):

- MarketScan cohort: 13,160
- Medicare cohort: 2,709

COMPARISON (# IN THE GROUP):

- MarketScan cohort: 106,361
- Medicare cohort: 17,639

FOLLOW UP PERIOD: Through outcome occurrence or death

RESULTS:

- There were no differences between metronidaxole-with-fluroquinolone and amoxicillin-clavulante in the MarketScan cohort for all outcomes:
    - One-year hospital admission (risk difference [RD] 0.1; 95% CI, –0.3 to 0.6)
    - One-year urgent surgery (RD 0.0; 95% CI, –0.1 to 0.1)
    - One-year risk of CDI (RD 0.0; 95% CI, –0.1 to 0.1)
    - Three-year elective surgery (RD 0.2; 95% CI, –0.3 to 0.7)
- The metronidazole-with-fluoroquinolone group had a higher one-year risk of CDI compared to the amoxicillin-clavulante group in the Medicare cohort (RD 0.6; 95% CI, 0.2 to 1.0; number needed to treat to harm: 167).
- There were no differences between metronidazole-with-fluroquinolone and amoxicillin-clavulante in the Medicare cohort for one-year hospital admission, one-year risk for urgent surgery, and three-year elective surgery.

LIMITATIONS:

- Antibiotic prescribing data was not included; thus, identification of patients and outcomes are based solely on diagnostic codes and reimbursement from filling a prescription.

- Multitude of possible confounders, such as patient compliance, were not controlled for.
- Not all harms of antibiotic therapy were considered such as common side effects (e.g., GI upset) to more severe adverse events (e.g., drug-induced liver injury or tendon rupture).

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Decreased Fetal Movements: A Cause for Concern?

Evaluation of Pregnancy Outcomes Among Women with Decreased Fetal Movements

Turner JM, Flenady V, Ellwood D, et al. Evaluation of pregnancy outcomes among women with decreased fetal movements. *JAMA Netw Open*. 2021; 4(4): e215071.

KEY TAKEAWAY: Decreased fetal movements (DFM) are not associated with an increased risk of stillbirth but are associated with an increased risk of small for gestation age (SGA) births, labor inductions, and emergency cesarean delivery.

STUDY DESIGN: Eleven-year retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Normal fetal movements are indicators of fetal well-being and DFM are associated with adverse outcomes, but it is unknown if DFM can be used as a predictor of stillbirth.

PATIENTS: Women with singleton pregnancies >28 weeks' gestation without a congenital anomaly

INTERVENTION: Decreased fetal movements

CONTROL: Normal fetal movements

OUTCOME: Incidence of stillbirth

Secondary Outcomes: Induction of labor, emergency cesarean delivery, SGA, composite of severe perinatal outcomes (SCPO; NICU admission, severe acidosis, 5-minute Apgar <4, stillbirth, and neonatal death)

METHODS (BRIEF DESCRIPTION):

- Inclusion Criteria: Singleton pregnancy, no known congenital anomaly, EGA ≥28 weeks
- Women with DFM and intrauterine demise at initial presentation were excluded.
  - DFM defined as decreased fetal movement frequency or strength, complete absence of fetal movement, or a deviation in movement pattern as observed by the expectant mother.
- Two management protocols were used to evaluate fetal wellbeing of those with DFM:
  - 2009–2016: Fetal wellbeing was evaluated initially with electronic fetal heart rate (FHR) monitoring. Further evaluations were done at discretion of treating physician.
  - 2016–2019: In addition to continuous FHR monitoring all women were tested for evidence of fetal-maternal hemorrhage (Kleihauer Betke test) then a determination was made to use or not use ultrasound to assess fetal wellbeing. Specific criteria used to determine when to use ultrasound were not given.

INTERVENTION (# IN THE GROUP): 8,821

COMPARISON (# IN THE GROUP): 92,776

FOLLOW UP PERIOD: Followed through pregnancy delivery

RESULTS:

Primary Outcome –

- DFM was not associated with higher odds of stillbirth (Adjusted Odds Ratio [aOR] 0.54; 95% CI, 0.23–1.3).

Secondary Outcomes –

- Pregnancies with DFM compared to normal fetal movement were at higher risk for:
  - Induction of labor (aOR 1.6; 95% CI, 1.5–1.7)
  - Emergency caesarean delivery (aOR 1.2; 95% CI, 1.1–1.3)
  - SGA (aOR 1.1; 95% CI, 1.0–1.3)
  - SCPO (aOR 1.1; 95% CI, 1.0–1.3)
- An increased odds of stillbirth occurred in patients with ≥2 presentations for DFM (aOR 1.6; 95% CI, 0.5–5.4).
- Odds of stillbirth were significantly greater in women with ≥2 presentations for DFM compared to those with only one (aOR 5.0; 95% CI, 0.98–25).

LIMITATIONS:

- There is no universally agreed upon definition of DFM.
- Maternal perception of fetal movements is highly subjective.
- Duration of each episode of DFM was not recorded.
- Study site implemented new policies during the study period resulting in an increased number of women who presented with DFM.
- Media campaigns increased during the study period resulting in a greater number of presentations of DFM.

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To Anticoagulate or Not? Low Dose Edoxaban in the Elderly

Low-Dose Edoxaban in Very Elderly Patients with Atrial Fibrillation

Okumura K, Akao M, and Yoshida T etal. Low-Dose Edoxaban in Very Elderly Patients with Atrial Fibrillation. *N Engl J Med*. 2020; 383(18):1735–1745.

KEY TAKEAWAY: Daily 15 mg edoxaban reduces the risk of stroke and systemic embolic events more than placebo in elderly Japanese adults. Edoxaban does not increase the risk of major bleeding events but does increase the risk of GI and overall bleeding.

STUDY DESIGN: Phase III, multicenter, randomized double-blinded placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The ENGAGE AF-TIMI 48 study previously demonstrated noninferiority of edoxaban to warfarin for stroke prevention and superiority for preventing bleeding in nonvalvular atrial fibrillation patients. Low dose edoxaban was thought to possibly be a safe and effective option for preventing stroke in the very elderly population who have a high risk for bleeding.

PATIENTS: Elderly Japanese patients with nonvalvular atrial fibrillation

INTERVENTION: 15 mg edoxaban

CONTROL: Placebo

OUTCOME: Efficacy Outcome – Stroke or systemic embolism

Safety Outcome – Major bleeding

Secondary Outcomes – Composite of stroke, systemic embolism, and death; all bleeding

METHODS (BRIEF DESCRIPTION):

- Patients were ≥80 years old (mean 87 years old) living in Japan with a history of nonvalvular atrial fibrillation with EKG or CHADS2 score of at least two.
  - 42% male
  - Not candidates for standard regimen of oral anticoagulants due to history of bleeding, low body weight, or low creatinine clearance.
- The treatment group received daily 15 mg edoxaban and was compared to the control who received placebo.
- Outcomes were evaluated with in-person medical office visits every four weeks until 48 weeks, then every eight weeks until trial completion.
- Event-driven study with events adjudicated by an independent committee with a goal of 65 stroke events.

INTERVENTION (# IN THE GROUP): 341

COMPARISON (# IN THE GROUP): 340

FOLLOW UP PERIOD: Median of 466 days

RESULTS:

Primary Outcomes –

- The treatment group was less likely to experience a stroke or systemic embolism event compared to the placebo group (2.3% vs 6.7%, respectively; HR 0.34; 95% CI, 0.19–0.61).
- The treatment group was less likely to experience significant bleeding risk compared to the placebo group (3.3% vs 1.8%, respectively; HR 1.9; 95% CI, 0.90–3.9).

Secondary Outcomes –

- The treatment group was more likely to experience GI bleeding than the placebo group (2.3% vs 0.8%, respectively; HR 2.9; 95% CI, 1.0–7.9).
- The treatment group was not more likely to experience stroke, systemic embolism, or cardiovascular death than the placebo group.
- The treatment group was more likely to experience all bleeding events than the placebo group (63% vs 45%, respectively; HR 1.4; 95% CI, 1.1–1.6).

LIMITATIONS:

- Funded by drug manufacturer.
- Many discontinued from study due to adverse events.
- Homogenous population.
- Patients were included in safety data if even just one dose of edoxaban given (data collected up to 3 days after last dose).

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