GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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Analyzing the Impact of Opioid Stewardship Programs on Racial Disparities in Opioid Prescription Practices

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Disparities in Emergency Department and Urgent Care Opioid Prescribing Before and After Randomized Clinician Feedback Interventions

Crowley AP, Sun C, Yan XS, et al. Disparities in emergency department and urgent care opioid prescribing before and after randomized clinician feedback interventions. *Acad Emerg Med.* 2023;30(8):809-818. doi:10.1111/acem.14717

KEY TAKEAWAY: Prescribers in the emergency department (ED) and urgent care (UC) settings are more likely to prescribe ≤10 opiate pills to Black and Hispanic patients compared to White patients. Combined feedback treatment resulted in more patients being prescribed ≤10 opiate pills compared to usual care. Peer comparison feedback and individual audit feedback did not affect the number of prescribed pills.

STUDY DESIGN: Four study arms, cluster randomized controlled trial (RCT)

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Ethnic and racial disparities in opioid prescribing have been reported when compared to White patients. These inequalities may be more prominent in ED and UC settings. While opioid stewardship programs (OSPs) aim to promote proper opioid prescription practices, including misuse, overuse, and abuse, considerations for already underserved patients should be considered to prevent a wider disparity. This study reviewed different modes of OSPs to determine if such programs add to the challenge of removing opioid prescribing discrepancies between different demographics.

PATIENTS: Adult patients of different races who received opioid prescription

INTERVENTION: Prescribing practices feedback

CONTROL: Usual care

PRIMARY OUTCOME: Likelihood of low-pill prescription

METHODS (BRIEF DESCRIPTION):

- The study was conducted over six months and included 438 physicians, physician assistants (PAs), and nurse practitioners (NPs) in 21 EDs and 27 UCs at Sutter Health.
- Patients ≥18 years old, who presented to the ED or UC without being admitted and received an opioid prescription were included in the study.
- Patients <18 years old, pregnant, were admitted, or did not receive an opioid prescription were excluded from the study.
- The intervention consisted of combined feedback, individual audit feedback, and peer comparison feedback.
- Usual care without an OSP in place was identified as the control.
- Opioid prescribing patterns were recorded at baseline and at six months.
- The primary outcome of the analysis was the factors associated with the likelihood of a low-pill prescription.
    - These factors include the four study arms (usual care, individual audit feedback, peer comparison feedback, and combined feedback) as well as the patient's race/ethnicity (Black non-Hispanic, Asian non-Hispanic, Hispanic, White non-Hispanic, and other).
- Low pill count (LPC) was defined as ≤10 pills. Medium pill count was defined as 11–19 pills. High pill count (HPC) was defined as ≥20 pills.
- Mixed-effects models determined association between patient characteristics (race, ethnicity) and LPC prescriptions at baseline and during opioid stewardship interventions.

INTERVENTION (# IN THE GROUP): 16,556

COMPARISON (# IN THE GROUP): 5,097

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- Patients in the combined feedback treatment group were more likely to receive an LPC during the intervention period compared to usual care (odds ratio [OR] 1.9; 95% CI, 1.3–2.8).
- There was no significant difference in pill prescription for peer comparison feedback and individual audit feedback group during the intervention period compared to usual care.
    - Peer comparison feedback (OR 1.3; 95% CI, 0.9–1.9)

    - Individual audit feedback (OR 0.99; 95% CI, 0.92–1.9)
- Black patients were significantly more likely to receive an LPC at baseline compared to White patients (OR 1.2; 95% CI, 1.1–1.3).
- Black patients were significantly more likely to receive an LPC during the intervention compared to White patients (OR 1.4; 95% CI, 1.1–1.9).
- Hispanic patients were significantly more likely to receive an LPC during the intervention only (OR 1.2; 95% CI, 1.0–1.5).

LIMITATIONS:

- Post-hoc analysis of this intervention was not designed to investigate disparities.
- The trial was conducted in a single health system in the western USA but amongst 48 sites with different leadership and policies.
- Pain control data was not available.
- No data on clinician's race or their perceptions of race.
- The minority sample size was too small.
- The intervention period (6 months) may be too short.
- The main trial had minor imbalances in race, insurance, and income, which were subsequently not adjusted in this analysis; subgroups in this study were not rerandomized.

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Reflecting on Our Practices: Access to Care for People with Opioid Use Disorder

Examining Access to Primary Care for People with Opioid Use Disorder in Ontario, Canada: A Randomized Clinical Trial

Spithoff S, Mogic L, Hum S, Moineddin R, Meaney C, Kiran T. Examining Access to Primary Care for People With Opioid Use Disorder in Ontario, Canada: A Randomized Clinical Trial. *JAMA Netw Open.* 2022;5(9):e2233659. Published 2022 Sep 1. doi:10.1001/jamanetworkopen.2022.33659

KEY TAKEAWAY: Family physicians were less likely to offer a new patient appointment to a patient with opioid use disorder than a patient with diabetes.

STUDY DESIGN: Randomized clinical trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: There is a growing population of individuals with opioid use disorder (OUD) in the US and Canada. Previous studies have found that patients with OUD who were enrolled with a primary care physician were more likely to receive preventative screening. Despite this, individuals with OUD have poor access to primary care and have difficulty finding a new physician. This study aimed to determine if family physicians are less likely to accept people with OUD as new patients than people with diabetes.

PATIENTS: Family physicians in Ontario Canada

INTERVENTION: Individual receiving treatment for OUD

CONTROL: Individual receiving treatment for diabetes

PRIMARY OUTCOME: Total new patient appointment offers

Secondary Outcome: Sub-analysis of confounding variables

METHODS (BRIEF DESCRIPTION):

- A randomized clinical trial using a controlled audit study design.
- Family physicians were selected using publicly available data from the College of Physicians and Surgeons of Ontario (CPSO) website with a reported specialty in family medicine.
- Physicians with restricted practices and physicians not in independent practice (medical residents or trainees) were excluded from the study.
- The eligible physicians were allocated 1:1 to two different scenarios where the caller played the role of a patient with either OUD or diabetes.
- The caller followed a script for a patient with diabetes in treatment with an endocrinologist or played the role of a patient with OUD undergoing methadone treatment with an additional physician.
- Callers selected family physicians across Ontario asking for a new patient appointment.
- Family medicine clinics were phoned up to five times over six weeks and accepted call-backs up to six weeks after the first phone call.
- The primary outcome measured whether the caller was offered a new patient appointment with the physician contacted, or with another physician/nurse practitioner at the same clinic.
- The secondary outcomes investigated potential confounding factors including gender, population size, model of care, and time in practice.
- Statistical analysis was performed by comparing the proportions of patients offered an appointment for each scenario stratified by the above-listed confounding factors.

INTERVENTION (# IN THE GROUP): 198

COMPARISON (# IN THE GROUP): 185

FOLLOW-UP PERIOD: Six weeks

RESULTS:

Primary Outcome –

- A greater proportion of physicians offered a new patient appointment to a caller receiving diabetes treatment compared to a caller receiving OUD treatment (absolute difference 7.4%; 95% CI, 2.0–12.6).
- After controlling for confounding variables, a caller receiving diabetes treatment had greater odds of being offered a new patient appointment compared to a caller receiving OUD treatment (odds ratio [OR] 2.9; 95% CI, 1.3–6.8).

Secondary Outcome –

- Women, as well as physicians practicing in larger centers, in a non-team model, and physicians with more years in practice, were less likely to offer a new patient appointment to a patient receiving

OUD treatment compared to a patient receiving diabetes treatment.

- Women (absolute difference 9.6%; 95% CI, 2.8–16.3)
- Physicians practicing in larger centers (absolute difference 9.1%; 95% CI, 3.4–15)
- Non-team model (absolute difference 6.7%; 95% CI, 1.0–12)
- Physicians with more years in practice (absolute difference 11%; 95% CI, 3.8–18)
- Findings were not significant for men, physicians in more rural areas, in team-based practices, and with fewer years in practice.

LIMITATIONS:

- Many participants after allocation and analysis showed no statistical difference in reasons for exclusion between the two groups.
- Possible that reception staff are authorized to accept new patients and the decision was not the physician's.
- Study conducted during the COVID-19 pandemic, which may have led to low rates of new patient acceptance.
- The caller was not blinded.
- May not be generalizable outside Ontario Canada.

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Antenatal Steroids for Late-Preterm Births: No Reduction in Neonatal Respiratory Complications

Late-Preterm Antenatal Steroids for Reduction of Neonatal Respiratory Complications: A Randomized Controlled Trial

Yenuberi H, Ross B, Sasmita Tirkey R, et al. Late-Preterm Antenatal Steroids for Reduction of Neonatal Respiratory Complications: A Randomized Controlled Trial. *Obstet Gynecol.* 2024;143(4):468-474. doi:10.1097/AOG.0000000000005520

KEY TAKEAWAY: Betamethasone administered in the late-preterm period (34–36 6/7 weeks gestation) to those at risk for preterm delivery does not reduce the need for neonates requiring treatment for respiratory distress.

STUDY DESIGN: Single-center, triple-blind, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Antenatal corticosteroids are the standard of care for preterm deliveries before 34 weeks of gestation. This practice is supported by continuous evidence demonstrating that antenatal corticosteroids significantly reduce the incidence of severe respiratory distress syndrome (RDS) and neonatal mortality in this population. However, the benefits of antenatal corticosteroids for late-preterm deliveries (34–36 6/7 weeks gestation) remain unclear. The data on their efficacy in this group are inconsistent, and there are concerns about potential neonatal and maternal adverse effects. This study aimed to evaluate the impact of antenatal corticosteroids on neonatal respiratory complications in late-preterm births.

PATIENTS: Pregnant women 34–36 6/7 weeks gestation

INTERVENTION: Betamethasone

CONTROL: Placebo

PRIMARY OUTCOME: Incidence of neonatal respiratory complications

Secondary Outcome: Neonatal or maternal complication

METHODS (BRIEF DESCRIPTION):

- 847 pregnant women with singleton or twin gestation at risk of preterm delivery in southern India were enrolled in the study.
- Clinical criteria for anticipation of early delivery include preterm pre-labor rupture of membranes, preterm labor (cervix dilated more than 3 cm or >75% effaced), gestational diabetes mellitus, preeclampsia, fetal growth restriction, or oligohydramnios.
- Participants were randomized to receive either two doses of intramuscular 12 mg betamethasone or 3 mL of placebo (sterile water), administered 24 hours apart.
    - If delivery was imminent, the second dose was administered 12 hours from the first dose.
- The medication administrator, investigators, and participants were blinded to the groups, and the intervention identities were only revealed after the statistical analysis was completed.
- Data was collected on both maternal and neonatal outcomes.
- Neonate requiring treatment for respiratory distress in the form of oxygen or continuous positive airway pressure or mechanical ventilation for at least two hours within the first 72 hours of life was measured as the primary outcome.
- Secondary outcomes included transient tachypnea of the newborn, respiratory distress syndrome, necrotizing enterocolitis, sepsis, hyperbilirubinemia, hypoglycemia, stillbirth, and early neonatal death.
- Maternal secondary outcomes included chorioamnionitis, postpartum hemorrhage, puerperal fever, and length of hospitalization.

INTERVENTION (# IN THE GROUP): 423

COMPARISON (# IN THE GROUP): 424

FOLLOW-UP PERIOD: Until delivery or immediately post-birth

RESULTS:

Primary Outcome –

- Betamethasone does not reduce the need for treating respiratory distress in neonates compared to placebo (4.9% vs 4.8%, respectively; relative risk [RR] 1.0; 95% CI, 0.57–1.8).

Secondary Outcome –

- There were no statistically significant differences for any of the secondary neonatal or maternal outcomes.

LIMITATIONS:

- The study was terminated early due to futility based on interim analysis.

- 22 participants (2% of all participants) were lost to follow-up.
- Only about 60% of participants received both doses of the study drug as per protocol.
- One-quarter of participants delivered at term, which could have influenced the primary outcome results.
- The study was conducted at a single center in India, which may limit generalizability to other populations.

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Does a Higher Transfusion Threshold Improve Mortality in MI Patients?

Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia

Carson JL, Brooks MM, Hébert PC, et al. Restrictive or Liberal Transfusion Strategy in Myocardial Infarction and Anemia. *N Engl J Med.* 2023;389(26):2446-2456. doi:10.1056/NEJMoa2307983

KEY TAKEAWAY: A liberal transfusion threshold of 10 g/dL does not reduce mortality or recurrent myocardial infarction (MI) compared to a transfusion threshold of 7 g/dL in patients with MI and anemia at 30 days.

STUDY DESIGN: Randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Current practice guidelines recommend transfusion at a Hgb threshold of 7 g/dL or 8 g/dL if the patient has congestive heart failure (CHF). There is no current consensus on the hemoglobin (Hgb) threshold for patients with an MI. This international study investigates the risk of reinfarction or death in patients with an MI and anemia utilizing a higher transfusion threshold of 10.

PATIENTS: MI patients with anemia

INTERVENTION: Transfusion 10 g/dL

CONTROL: Transfusion 7–8 g/dL

PRIMARY OUTCOME: Death or recurrent MI

METHODS (BRIEF DESCRIPTION):

- The study was conducted in the US, Canada, France, New Zealand, Brazil, and Australia.
- 3,504 inpatient individuals, >18 years old with MI and HgB <10 g/dl were included in the study.
  - The average patient in the study was 72 years old, and 46% were female.
- Exclusion criteria included patients who did not have an MI, had uncontrolled bleeding, were receiving palliative treatment, were scheduled for cardiac surgery on the same admission, or declined to receive blood transfusions.
- Patients in the intervention group received a transfusion of 2.5±2.3 units at a threshold of <10 g/dl Hgb.
- Patients in the control group received a transfusion of 0.7±1.6 units for the restrictive population at a threshold of 7–8 g/dl Hgb.
- One unit of packed red blood cells (PRBCs) was administered at a time in each group followed by measurement of Hgb Levels, with the liberal group receiving enough units to maintain them above a Hgb level of 10 g/dl at all times.
- The primary outcome was measured by the incidence of reinfarction or cessation of vital signs.

INTERVENTION (# IN THE GROUP): 1,755

COMPARISON (# IN THE GROUP): 1,749

FOLLOW-UP PERIOD: 30 days

RESULTS:

Primary Outcome –

- There was no reduction in reinfarction for MI patients who received transfusions at 10 g/dL compared to those who received transfusions at 7–8 g/dL (risk ratio [RR] 1.2; 95% CI, 0.99–1.3).
- There was no reduction in death for MI patients who received transfusions at 10 g/dL compared to those who received transfusions at 7–8 g/dl (RR 1.2; 95% CI, 0.96–1.5).

LIMITATIONS:

- This study was unmasked possibly altering any clinical decision-making, additional interventions, or classification of the cause of death.
- Less than half the deaths were classified as cardiac, thus unclear determination of transfusion truly altered mortality outcomes.
- The <10 g/dL transfusion threshold adherence was only moderate, likely due to clinical discretion by the medical team.

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SGLT2 Inhibitors Found to Reverse Steatosis in Non-Alcoholic Liver Disease

Outcomes of Various Classes of Oral Antidiabetic Drugs on Nonalcoholic Fatty Liver Disease

Jang H, Kim Y, Lee DH, et al. Outcomes of Various Classes of Oral Antidiabetic Drugs on Nonalcoholic Fatty Liver Disease. *JAMA Intern Med.* 2024;184(4):375-383. doi:10.1001/jamainternmed.2023.8029

KEY TAKEAWAY: Sodium-glucose co-transport (SGLT2) inhibitors are preferred as oral anti-diabetic agents in patients with steatosis associated with non-alcoholic liver disease (NAFLD) and type 2 diabetes (T2DM).

STUDY DESIGN: Retrospective nonrandomized interventional cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: The incidence of fatty liver disease in patients with T2DM is high. T2DM is also known to accelerate liver steatosis. Several studies have shown that NAFLD can progress to steatohepatitis, liver cirrhosis, and eventually to liver cancer. Historically, there have been no investigations concerning which oral anti-diabetic drug can reduce the progression of steatosis in patients with T2DM and NAFLD. This study aims to investigate various classes of oral anti-diabetic agents and their effect on liver steatosis regression and the incidence of other liver-related adverse outcomes.

PATIENTS: Adults with hepatic steatosis and T2DM on oral anti-diabetic agents

INTERVENTION: SGLT2 inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, sulfonylurea

CONTROL: Not applicable

PRIMARY OUTCOME: NAFLD regression

Secondary Outcome: Adverse liver-related outcome

METHODS (BRIEF DESCRIPTION):

- Data was obtained using a nationwide database from the National Health Insurance Service (NHIS) in South Korea.
- Patient inclusion criteria: ≥19 years old, diagnosis of hepatic steatosis, T2DM, hepatic steatosis at baseline was defined as a (FLI) score of ≥60.
- Patient exclusion criteria: Individuals who used any antidiabetic drugs between January 2012 and September 2014, individuals who used ≥3 classes of antidiabetic medications, used insulin or GLP-1 receptor agonists for ≥90 days, diagnosed with any cancer or liver disease, were on drugs affecting NAFLD regression, consumed significant alcohol (≥210 g/week for males and ≥140 g/week for females).
- Four oral antidiabetic drugs, without dosage specifications, were compared to each other in combination with metformin: SGLT2 inhibitors, thiazolidinediones, DPP-4 inhibitors, and sulfonylureas.
- Participants were required to adhere to the regimen ≥80% for 90 consecutive days
- To investigate NFALD regression, a fatty liver index (FLI) score was used. FLI is based on metrics such as waist circumference, body mass index (BMI), triglyceride levels, and gamma-glutamyl-transferase (GGT) to evaluate the presence of steatosis.
- NAFLD regression was defined as a reduction in FLI score to <30.

INTERVENTION (# IN THE GROUP):

- SGLT2: 9,470
- Thiazolidinediones: 2,191
- DPP-4: 55,324
- Sulfonylurea: 13,193

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Four years

RESULTS:

Primary Outcome –

- All classes of antidiabetic drugs were associated with an increased incidence of NAFLD regression compared with sulfonylureas.
  - SGLT2 inhibitor (adjusted subdistribution hazard ratio [ASHR] 2.0; 95% CI, 1.8–2.3)
  - Thiazolidinedione (ASHR 1.7; 95% CI, 1.4–2.1)
  - DPP-4 inhibitor (ASHR 1.5; 95% CI, 1.3–1.6)
- SGLT2 inhibitors were associated with an increased incidence of NAFLD regression when compared with:
  - Thiazolidinediones (ASHR 1.4; 95% CI, 1.1–1.8)
  - DPP-4 inhibitors (ASHR 1.5; 95% CI, 1.3–1.6)

Secondary Outcome

- SGLT2 inhibitors were associated with lower incidence rates of adverse liver-related outcomes when compared with sulfonylureas (ASHR 0.37; 95% CI, 0.17–0.82).

LIMITATIONS:

- Only a selective patient population was used to establish poor glycemic control such as only patients with T2DM who were on dual therapy with metformin.
- Hepatic steatosis associated with non-alcoholic liver disease was determined by FLI index as opposed to superior imaging modalities or a liver biopsy. However, the FLI index is convenient in outpatient settings that often lack resources.
- Oral anti-diabetics agents may affect other variables such as BMI which can affect FLI score.

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To Treat or Not to Treat: Convalescent Plasma in COVID-19-Induced ARDS

Convalescent Plasma for Covid-19-Induced ARDS in Mechanically Ventilated Patients

Misset B, Piagnerelli M, Hoste E, et al. Convalescent Plasma for Covid-19-Induced ARDS in Mechanically Ventilated Patients. *N Engl J Med.* 2023;389(17):1590-1600. doi:10.1056/NEJMoa2209502

KEY TAKEAWAY: Administration of convalescent plasma to patients with COVID-19-induced ARDS on mechanical ventilation reduces the risk of 28-day mortality compared to standard care.

STUDY DESIGN: Randomized, controlled open-label trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: It is thought that transfusions with convalescent plasma may give passive immunization to patients with COVID-19. However, there is limited data pertaining to treating mechanically ventilated patients with ARDS in patients with COVID-19. This study seeks to determine how treatment with convalescent plasma affects mortality in such patients.

PATIENTS: Patients with COVID-19-induced ARDS on mechanical ventilation

INTERVENTION: Convalescent plasma with neutralizing antibodies

CONTROL: Standard care

PRIMARY OUTCOME: Short-term mortality

Secondary Outcome: Long-term mortality, adverse events, organ failure, use of organ support, inflammatory and antibody response, length-of-stay

METHODS (BRIEF DESCRIPTION):

- The study included 475 participants and was conducted in Belgium.
- Inclusion criteria: Adult ICU patients with COVID-19-induced ARDS on mechanical ventilation for <5 days, with a frailty score <6.
- Exclusion criteria: Participation in other COVID-19 trials, pregnancy, history of previous transfusion reactions, and a medical decision to limit therapy.
- Average Demographics
  - Median age: 64 years old
  - 68% Males
  - Mean COVID-19 vaccination status: 9.7%
  - Additional comorbidities: Hypertension, congestive heart failure, chronic obstructive pulmonary disease (COPD), diabetes, asthma
- Within 24 hours of inclusion into the study, intervention group participants received one dose of two units of convalescent plasma with neutralizing antibody titers of 1:320 or 1:160 during plasma shortages.
- The control group received standard care without any placebo.
- Standard of care included international guidelines related to the administration of fluids, vasopressors, medications, and ventilator settings.
- The primary outcome measured the difference in the incidence of mortality at day 28.
- The secondary outcomes measured adverse events, antibody and inflammatory responses, measures of end-organ impact, length of stay, and incidence of long-term mortality at 90 and 365 days.

INTERVENTION (# IN THE GROUP): 237

COMPARISON (# IN THE GROUP): 238

FOLLOW-UP PERIOD: 365 days

RESULTS:

Primary Outcome –

- Convalescent plasma significantly decreased mortality at 28 days compared to standard care (35% vs 45%, respectively; p=.03).

Secondary Outcome –

- Convalescent plasma did not significantly increase adverse events compared to standard care and no adverse events were deemed to be directly related to the administration of convalescent plasma.
- There was no difference in mortality at 90 days between convalescent plasma and standard care.
- There was no difference in mortality at 365 days between convalescent plasma and standard care.
- Other secondary outcomes including length of stay, antibody responses, and organ support were also similar between groups.

LIMITATIONS:

- The study was unblinded which could have led to inter-group differences in care.

- Generalizability may be limited as neutralizing antibodies were collected during previous COVID-19 waves and may be unhelpful against newer variants.
- The neutralizing antibody titers were not measured against an international standard.
- While the study showed a statistically significant difference in mortality at 28 days, it was underpowered to assess the difference in survival time, which may be a more clinically important outcome.
- The difference in mortality at 28 days is lower, however, the difference in the survival curve is not statistically significant due to the study being underpowered.

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