GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Gabapentinoids and COPD: Is It Getting Harder and Harder to Breathe?

Gabapentinoids and COPD: Is It Getting Harder and Harder to Breathe?

Gabapentinoids and Risk for Severe Exacerbation in Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study

Rahman AA, Dell'Aniello S, Moodie EEM, et al. Gabapentinoids and Risk for Severe Exacerbation in Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study. *Ann Intern Med.* 2024;177(2):144-154. doi:10.7326/M23-0849

KEY TAKEAWAY: The use of gabapentinoids for any indication is associated with an increased risk of hospitalization for severe chronic obstructive pulmonary disease (COPD) exacerbation.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Gabapentinoids are indicated for the treatment of epilepsy and neuropathic pain and have increased in popularity for the management of a multitude of pain-related conditions as they are perceived to be safer than opioids. This is particularly concerning as they have a myriad of adverse effects including nervous system depression, sedation, and respiratory depression. For patients with COPD, these side effects could have detrimental consequences. This retrospective cohort attempts to assess the association between gabapentinoid use and hospitalization from severe COPD exacerbation.

PATIENTS: Adults with COPD

INTERVENTION: Gabapentinoid use

CONTROL: No gabapentinoid use

PRIMARY OUTCOME: COPD exacerbation

METHODS (BRIEF DESCRIPTION):

- The cohort was identified from three outpatient prescription databases including The Régie de l'assurance maladie du Québec (RAMQ), the Maintenance et exploitation des données pour l'étude de la clientele hospitalière, and the Institut de la statistique du Québec. Together, these databases encompass approximately 43% of the entire Quebec population.
- All patients ≥55 years old with COPD, identified as patients who received three or more prescriptions for respiratory medications (long-acting beta-agonist, long-acting muscarinic antagonist, combination, or inhaled corticosteroid) on two separate occasions within a one year period from 1/1/1994–12/31/2015 who had never previously received gabapentinoids were included in the study.
- Patients diagnosed with asthma during any hospitalization or patients receiving medications associated with asthma (nedocromil, ketotifen, cromolyn, or anti-leukotrienes) were excluded.
- Gabapentinoid users were identified by receipt of a new prescription for a gabapentinoid for the diagnosis of epilepsy, neuropathic pain, or chronic pain.
- Time-conditional propensity score (TCPS) matching was utilized to match individuals in the gabapentinoid group with similar non-gabapentinoid users based on comorbid conditions, overall health (defined as number of hospitalizations and number of medication classes prescribed), age, sex, and region of residence.
- Baseline characteristics of patients included a mean age in the mid-70s, of whom approximately 57% were female, medical comorbidities including hypertension, diabetes, and coronary artery disease were common as was polypharmacy with nonsteroidal anti-inflammatories, opioids, and/or benzodiazepines.
- The primary outcome was severe COPD exacerbation, defined as hospitalization or death from COPD, determined by inpatient ICD9 and ICD10 codes.

INTERVENTION (# IN THE GROUP): 13,504

COMPARISON (# IN THE GROUP): 13,504

FOLLOW-UP PERIOD: Mean 1.5 years

RESULTS:

Primary Outcome –

- Gabapentinoid use for all three indications was associated with a statistically significant increase in the risk of hospitalization for severe COPD exacerbation (adjusted hazard ratio [aHR] 1.4; 95% CI, 1.3–1.5).
- When broken down by indication for use, gabapentinoid increased the risk for hospitalization in each of the following groups:
  - Chronic pain (aHR 1.5; 95% CI, 1.3–1.7)

- Neuropathic pain (aHR 1.4; 95% CI, 1.2–1.5)
- Epilepsy (aHR 1.6; 95% CI, 1.1–2.3)

LIMITATIONS:

- COPD in this study was defined using a national prescription database based on common medications prescribed for COPD and not ICD10 codes, potentially leading to misdiagnoses as there can be overlap between asthma and COPD medications.
- Adherence to medications was not assessed.
- This study was vulnerable to residual confounding including lack of information on current or previous tobacco use as well as opioid use.

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How Much Do We Know About Amoxicillin-Induced Aseptic Meningitis?

Amoxicillin-Induced Aseptic Meningitis: Clinical Features, Diagnosis, and Management

Fan Z, He Y, Sun W, Li Z, Ye C, Wang C. Amoxicillin-induced aseptic meningitis: clinical features, diagnosis, and management. *Eur J Med Res.* 2023;28(1):301. Published 2023 Aug 27. doi:10.1186/s40001-023-01251-y

KEY TAKEAWAY: Diligent medication history of patients with suspected meningitis may improve earlier detection of amoxicillin-induced aseptic meningitis (AIAM).

STUDY DESIGN: Systematic review and meta-analysis of 20 case reports, case series, original studies, and clinical trials (N=22).

LEVEL OF EVIDENCE: STEP 2 (downgraded due to small sample size)

BRIEF BACKGROUND INFORMATION: The diagnosis of drug-induced aseptic meningitis (DIAM) is underreported but when suspected is often associated with amoxicillin. Most clinical features of AIAM have not been formally developed and it remains a widely unknown adverse event.

PATIENTS: Adults with AIAM

INTERVENTION: Clinical characteristics of AIAM

CONTROL: Not applicable

PRIMARY OUTCOME: Meningitis symptom recovery

METHODS (BRIEF DESCRIPTION):

- Data was extracted by two independent authors. If the patient had several episodes of AIAM, the most recent episode was used.
- Demographics include 22 patients, nine females and 13 males with a median age of 63 years old. Patients were from Europe, North America, and Asia.
- AIAM was summarized as the timely association between amoxicillin-based products, CSF leukocytosis, negative culture, and length of symptom recovery after drug withdrawal.
- Patients received either amoxicillin or amoxicillin clavulanic acid as treatment options with doses either unidentified or ranging between 500 mg to 2 g.
- The 22 patients included in the meta-analysis were analyzed for symptoms and time to symptom resolution.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Three hours to seven days after drug administration

RESULTS:

Primary Outcome –

- The most common symptoms included: Fever (86%), headache (82%), nuchal rigidity (32%), photophobia (27%), and nausea (27%).
- Upon CSF analysis, glucose was normal in 100% of cases, protein was elevated in 95% of cases, leukocytosis in 100% of cases, and red blood cells in 14% of cases.
- MRI showed no abnormalities in 94%.
- Symptoms of AIAM present between three hours and seven days post-administration.
- Symptomatic recovery between 12 hours and 14 days in 20 patients after discontinuing amoxicillin/amoxicillin-clavulanate.

LIMITATIONS:

- The sample size was small.
- The study looked mainly at case series and single case reports.

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Rising Prevalence of Pregestational Diabetes Mellitus Increases Maternal Risk During Obstetric Deliveries

Trends in Delivery Hospitalizations with Pregestational and Gestational Diabetes Mellitus and Associated Outcomes: 2000–2019

Gorsch LP, Wen T, Lonier JY, et al. Trends in delivery hospitalizations with pregestational and gestational diabetes mellitus and associated outcomes: 2000-2019. *Am J Obstet Gynecol.* 2023;229(1):63.e1-63.e14. doi:10.1016/j.ajog.2022.12.006

KEY TAKEAWAY: Pregestational diabetes has substantially increased, leading to increased maternal risk and the need for health optimization during pregnancy.

STUDY DESIGN: Repeated cross-sectional analysis

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Pregestational diabetes is a common condition causing adverse outcomes of pregnancy including pre-term and cesarean deliveries, shoulder dystocia, and hypertensive complications. Previous analyses showed a 50% increase in pregestational diabetes from 1993–2009. With the quadrupling prevalence of type 2 diabetes mellitus (T2DM), it is important to understand national trends to help guide effective primary care management during pregnancy.

PATIENTS: Adults delivering in hospitals

INTERVENTION: Delivery hospitalizations with diabetes

CONTROL: Delivery hospitalizations without diabetes

PRIMARY OUTCOME: National Trends in delivery hospitalizations

Secondary Outcome: Delivery outcomes associated with pregestational diabetes

METHODS (BRIEF DESCRIPTION):

- Adults 15–54 years old from the national inpatient sample between 2000–2019 who delivered in a hospital setting were included.
- Those with identified diabetes were compared to develop national trends as the intervention group.
- Patients were divided into groups by maternal age, race, payer type, clinical factors, hospital teaching status, and median ZIP code income quartile.
- The adverse outcomes of the intervention groups were compared to those without a diagnosis of diabetes mellitus (DM).
- Adverse delivery outcomes included pre-term delivery, operative vaginal or cesarean delivery, gestational hypertension (HTN) and preeclampsia, postpartum hemorrhage, shoulder dystocia, episiotomy, injury to anal sphincter, maternal morbidity, and non-transfusion severe maternal morbidity.
- Outcomes were measured using the National Cancer Institute's Join-point regression program, expressing patterns and trends as an average annual percent change (AAPC).
- Demographic, clinical, and hospital characteristics were compared between interventions and control group with Chi-square tests.

INTERVENTION (# IN THE GROUP):

- Type 1 diabetes mellitus (T1DM): 179,885
- T2DM: 430,544
- Gestational diabetes mellitus (GDM): 4,518,330
- Unspecified DM: 99,327

COMPARISON (# IN THE GROUP): 71,471,686

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- The average annual percent change of DM increased by 8.0% in deliveries for T2DM (CI, 6.9–9.2%), 3.9% in deliveries for unspecified DM (CI, 1.4–6.3%), 0.2% in deliveries for T1DM (CI, 0.8–1.3%).
- The prevalence of chronic DM complications increased from 2.7–5.6% with an annual change of 5.9% (CI, 3.7–8.0%).
- T1DM was more common in deliveries to adults with chronic HTN, asthma, or obesity, in urban teaching hospitals, and deliveries covered by private insurance.
- Prevalence of T2DM quadrupled and was more common in older adults, those covered by Medicaid, those with obesity or chronic HTN, and women identifying as non-Hispanic Black or Hispanic.
- Unspecified DM was more common in deliveries covered by Medicaid, diagnoses of asthma, obesity, or chronic HTN, and at urban teaching hospitals.

Secondary Outcome –

- Compared to non-diabetics, pregestational diabetes is associated with severe maternal morbidity,

cesarean deliveries, pre-term birth, shoulder dystocia, and hypertensive disorders of pregnancy.
- Deliveries with complications of shoulder dystocia, episiotomy, operative vaginal delivery, and anal sphincter injury decreased over the study period for both diabetics and non-diabetics.

LIMITATIONS:

- Clinical data was not analyzed including prenatal care, glucose, and medical management.
- Deliveries outside of the hospital setting are not assessed in the NIS database.
- Billing codes are not standard and subjective.
- Neonates were not evaluated after delivery.
- NIS had two database changes in sampling methods and billing coding.
- Patients were not followed over time.
- Population weights result in narrow confidence intervals compared to raw data.

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Recurrent Atrial Fibrillation: Will It Make a Comeback?

Atrial Fibrillation Recurrence in Patients with Transient New-Onset Atrial Fibrillation Detected During Hospitalization for Noncardiac Surgery or Medical Illness: A Matched Cohort Study

McIntyre WF, Vadakken ME, Connolly SJ, et al. Atrial Fibrillation Recurrence in Patients With Transient New-Onset Atrial Fibrillation Detected During Hospitalization for Noncardiac Surgery or Medical Illness: A Matched Cohort Study. *Ann Intern Med.* 2023;176(10):1299-1307. doi:10.7326/M23-1411

KEY TAKEAWAY: For patients who experienced episodes of transient, new-onset atrial fibrillation (AF) during hospitalization for either noncardiac surgery or medical illness, about one in three will have another episode in one year.

STUDY DESIGN: Matched cohort study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to limited generalizability and low power)

BRIEF BACKGROUND INFORMATION: Atrial fibrillation is the most common arrhythmia and determination of stroke risk is critical to provide appropriate pharmacotherapy. It is unclear if long-term anticoagulation is necessary if AF occurs in the context of surgery or reversible medical illness.

PATIENTS: Patients hospitalized for a non-cardiac surgery or medical illness

INTERVENTION: Patients with transient, new-onset AF

CONTROL: Matched controls

PRIMARY OUTCOME: AF detected lasting at least 30 seconds

Secondary Outcome: Duration of all AF episodes, adverse events

METHODS (BRIEF DESCRIPTION):

- Patients from three academic hospitals in Ontario, Canada with a mean age of 71 years old were included. 59% were male and 41% were female.
  - Inclusion criteria: $CHADS_2$ score of at least one or ≥65 years old
  - Exclusion criteria: History of AF before hospitalization, pacemaker/defibrillator or stroke, myocardial infarction (MI), heart failure, pericarditis, or arrhythmia.
- Patients with AF detected during initial hospitalization who returned to sinus rhythm and controls, matched for sex and age were recruited for the study.
- Three post-discharge assessments were done via telephone at one, six, and 12 months which involved an interview and a complete medical record review.
- A 14-day ECG patch was offered at one and six months.
- Outcomes were measured as:
  - Recurrent AF: Defined as lasting at least 30 seconds on an ECG patch or visualized on 12 lead ECG
  - Duration of all AF episodes
  - Adverse events included incidence of death, stroke, bleeding, embolism, and hospitalization for heart failure (HF) or MI within 12 months after enrollment.
- Data collection occurred via source documents.
  - Medications, new occurrences of AF (outside of study), death, stroke, bleeding, embolism, and hospitalization for heart failure or myocardial infarction.

INTERVENTION (# IN THE GROUP): 139

COMPARISON (# IN THE GROUP): 139

FOLLOW-UP PERIOD: One, six, and 12 months

RESULTS:

Primary Outcome –

- After one year of follow-up, recurrent AF was detected in 33% (95% CI, 25–41%) of those with transient, new-onset AF compared to only 5% (95% CI, 1.4–8.7%) in the control group.
- After one year of follow-up, patients who had transient AF had a 32% risk of AF (95% CI, 23–42%) compared to 3% in the matched control (95% CI, 0–6.4%).

Secondary Outcome –

- During follow-up, the median duration of all AF episodes in patients who had transient, new-onset AF was 7.9 hours (1.8–45); the median duration of AF in the matched control group was 9.8 hours (3.5–66).
- Adverse events within 12 months of enrollment:

- Transient, new-onset AF group: 11 patients died, one had a stroke, six had a bleeding event, two had a systemic embolism, three had HF events, and three had an MI.
- Matched control group: Seven patients died, one had a stroke, four had a bleeding event, and one had an HF event; no reported incidence of MI or embolism.

LIMITATIONS:

- Small sample size, which limits generalizability.
- Telephone assessments are subject to recall bias and are not an objective form of data collection.
- ECG monitoring was limited to 28 days total, therefore, the reoccurrence of AF could have occurred outside this window.
- Underpowered study that was unable to assess subgroups and other confounding factors that could have predisposed patients to recurrent AF.

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