GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of October 28 - November 1, 2024

SPOTLIGHT:
Dosing Matters in Migraine Patients

Dosing Matters in Migraine Patients

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Efficacy and Safety of Ubrogepant for Migraine: A Meta-Analysis of Randomized Controlled Studies

Wu SZ, Chen L. Efficacy and safety of ubrogepant for migraine: a meta-analysis of randomized controlled studies. *Int J Neurosci*. 2024;134(2):124-130. doi:10.1080/00207454.2022.2090351

KEY TAKEAWAY: Ubrogepant 50 mg is as efficacious as 100 mg in the treatment of acute migraines and has fewer adverse effects.

STUDY DESIGN: Meta-analysis of three randomized controlled trials (N=1,972)

LEVEL OF EVIDENCE: STEP 1

BRIEF BACKGROUND INFORMATION: Migraines are a common, chronic disease. Ubrogepant is a newer drug to treat acute migraine attacks. The effective treatment dosages have not been well established; however, it is an area of active research. Establishing the most effective treatment with the fewest side effects for the many people suffering from migraines would allow them to live more fulfilling lives.

PATIENTS: Migraine patients

INTERVENTION: Ubrogepant 50 mg

CONTROL: Ubrogepant 100 mg

PRIMARY OUTCOME: Pain relief

Secondary Outcome: Absence of migraine signs/symptoms, adverse events

METHODS (BRIEF DESCRIPTION):

- The three included studies were each conducted at multiple centers across the United States.
- Approximately 83% were female (only 2 out of 3 studies included data on patient sex), with a mean age of approximately 40 years old, and an overweight average BMI.
- Eligibility criteria:
  - Required patients studied to have migraine diagnosis (only patients with acute migraines were studied in the included literature)
  - Intervention with Ubrogepant 50 mg PO once, with control being Ubrogepant 100 mg PO once
  - Must be a randomized control trial
  - Measurement of the primary and secondary outcomes listed below
  - No specific demographic criteria
- The primary outcome measured pain relief as defined as pain-free for at least two hours with continued pain relief up to 24 hours.
  - No explanation was provided as to how pain was measured.
- The secondary outcomes measured migraine signs and symptoms as defined by the absence of photophobia at two hours, absence of phonophobia at two hours, absence of nausea at two hours, and adverse events including serious adverse events.
  - No explanation was provided as to how adverse events were measured or classified.

INTERVENTION (# IN THE GROUP): 976

COMPARISON (# IN THE GROUP): 996

FOLLOW-UP PERIOD: Not available

RESULTS:

Primary Outcome –

- 50 mg of ubrogepant was equivalent to 100 mg in pain relief at two hours (odds ratio [OR] 0.86; 95% CI, 0.64–1.2) and continued pain relief up to 24 hours (OR 0.76; 95% CI, 0.54–1.1).

Secondary Outcome –

- Ubrogepant 50 mg and 100 mg performed similarly in the absence of photophobia (OR 0.80; 95% CI, 0.63–1.0), phonophobia (OR 1.1; 95% CI, 0.82–1.4), and nausea (OR 1.0; 95% CI, 0.79–1.3) at two hours.
- Ubrogepant 50 mg reduced the risk of adverse events compared to ubrogepant 100 mg (OR 0.81; 95% CI, 0.67–0.99).
- Ubrogepant 50 mg and 100 mg have a comparable incidence of serious adverse events (OR 0.87; 95% CI, 0.40–1.9).

LIMITATIONS:

- The study was underpowered.
- Only the treatment of acute migraines was studied.
- Homogenous patient demographics suggest the findings may not extrapolate to other patients suffering from migraines.

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Enhanced Glycemic Control with Early Triple Therapy in T2DM: Insights from the PEAK Trial

Efficacy and Safety of Alogliptin-Pioglitazone Combination for Type 2 Diabetes Mellitus Poorly Controlled with Metformin: A Multicenter, Double-Blind Randomized Trial

Park JY, Lee J, Choi YH, et al. Efficacy and Safety of Alogliptin-Pioglitazone Combination for Type 2 Diabetes Mellitus Poorly Controlled with Metformin: A Multicenter, Double-Blind Randomized Trial. *Diabetes Metab J.* 2024;48(5):915-928. doi:10.4093/dmj.2023.0259

KEY TAKEAWAY: Early triple combination with metformin, pioglitazone, and alogliptin improves glycemic control compared to single add-on therapies for patients in South Korea.

STUDY DESIGN: Multicenter, three-arm parallel-group, double-blind, placebo-controlled randomized control trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Type 2 diabetes mellitus (T2DM) is a prevalent chronic condition often treated in primary care, however, less than one-third of patients achieve A1C control <6.5%. Previous research shows patients have a higher chance of achieving glycemic control with early combination therapy rather than metformin alone. To clarify guidelines in advancing to combination therapy in Asian populations, this study evaluated the efficacy and safety of adding thiazolidinedione pioglitazone and/or DPP-4 inhibitor alogliptin in patients unable to meet A1C goal on metformin alone.

PATIENTS: Adults with T2DM

INTERVENTION: Metformin + alogliptin + pioglitazone daily

CONTROL: Metformin + alogliptin + placebo or metformin + pioglitazone + placebo daily

PRIMARY OUTCOME: HbA1c

Secondary Outcome: Insulin resistance, β-cell function, BMI

METHODS (BRIEF DESCRIPTION):

- The study was conducted across 13 centers in South Korea from 1/30/2015 to 10/4/2018.
- Patients 19–75 years old, confirmed diagnosis of T2DM at least six months, BMI 18.5–45 kg/m², baseline HbA1c 7.0–10%, minimum fasting C-peptide level of 0.78 ng/mL, blood pressure up to 160/100 mmHg, and hemoglobin ≥12 g/dL (men) or ≥10 g/dL (women) were included in the study.
- Exclusion criteria:
  - Use of medications affecting blood glucose control
  - New York Heart Association Class III-IV heart failure
  - Known hypersensitivity to alogliptin or pioglitazone
- Demographic characteristics included a mean age of 59 years old and a mean HbA1c of 8.0% at baseline.
- There were no significant differences in metformin dose, BMI, blood pressure, or fasting C-peptide level at baseline.
- Patients were randomized into one of three groups:
  - Metformin + pioglitazone + placebo (Pio)
  - Metformin + alogliptin + placebo (Alo)
  - Metformin + alogliptin + pioglitazone (Alo+Pio)
- Primary outcome: Change in HbA1C measured from baseline to week 24.
- Secondary outcomes measured insulin resistance, β-cell function, and BMI
  - Insulin resistance was calculated using the Homeostatic Model Assessment for Insulin Resistance HOMA-IR. Normal values range from 0.5–1.4, with higher values correlated with increasing insulin resistance.
    - Measured at baseline and 24 weeks
  - β-cell function was calculated using the Homeostatic Model Assessment for β-cell function (HOMA-β). Normal values range from 100–200% with lower values correlated with decreased β-cell function.
    - Measured at baseline and 24 weeks
  - BMI change from baseline was analyzed using Kruskal-Wallis which produces a test statistic value *H* which can range from zero to a positive number, with higher values indicating a greater difference between groups.
    - Measured at baseline, 12 weeks, and 24 weeks

INTERVENTION (# IN THE GROUP): 70

COMPARISON (# IN THE GROUP):

- Alo: 75
- Pio: 69

FOLLOW-UP PERIOD: 12 and 24 weeks

RESULTS:

Primary Outcome –

- Alo + Pio significantly decreased HbA1c compared to Alo at 12 weeks (mean –1.1% vs –0.92%, respectively; *P*=.0001).
- Alo + Pio significantly decreased HbA1c compared to Pio at 12 weeks (mean –1.1% vs –0.63%, respectively; *P*=.0001).
- Alo + Pio significantly decreased HbA1c compared to Alo at 24 weeks (mean –1.4% vs –1.0%, respectively; *P*=.0001).
- Alo + Pio significantly decreased HbA1c compared to Pio at 24 weeks (mean –1.4% vs –0.84%, respectively; *P*=.0001).

Secondary Outcome –

- Alo + Pio significantly decreased insulin resistance compared to Alo at 24 weeks (mean –1.0 vs –0.41, respectively; *P*=.0003).
- Alo + Pio significantly decreased insulin resistance compared to Pio at 24 weeks (mean –1.0 vs –0.97, respectively; *P*=.0003).
- Alo + pio significantly improved β cell function compared to Alo at 24 weeks (mean 6.0 vs 9.0, respectively; *P*=.0042).
- Alo + pio significantly improved β cell function compared to Pio at 24 weeks (mean 6.0 vs 1.0, respectively; *P*=.0042).
- Alo + pio significantly decreased BMI compared to Alo at 12 weeks (mean 0.46 vs –0.03, respectively; *P*<.0001).
- Alo + pio significantly decreased BMI compared to Pio at 12 weeks (mean 0.46 vs 0.33, respectively; *P*<.0001).
- Alo + pio significantly decreased BMI compared to Alo + Pio at 24 weeks (mean 0.63 vs –0.05, respectively; *P*<.0001).
- Alo + pio significantly decreased BMI compared to Pio at 24 weeks (mean 0.63 vs 0.5, respectively; *P*<.0001).

LIMITATIONS:

- Relatively small sample size
- Poor generalizability to the United States population due to only South Korean Asian patients.
- Short follow-up period of only 24 weeks.
- No obese patients were included (mean BMI of 25).
- The majority of patients were male (57%).
- Aside from metformin, doses of medications used were not listed.

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Will D-Mannose Protect You from Your Next UTI?

D-Mannose for Prevention of Recurrent Urinary Tract Infection Among Women: A Randomized Clinical Trial

Hayward G, Mort S, Hay AD, et al. d-Mannose for Prevention of Recurrent Urinary Tract Infection Among Women: A Randomized Clinical Trial. *JAMA Intern Med.* 2024;184(6):619-628. doi:10.1001/jamainternmed.2024.0264

KEY TAKEAWAY: Daily D-mannose does not reduce urinary tract infections (UTIs) in adult women with recurrent UTIs in a primary care setting.

STUDY DESIGN: Two-group, double-blind randomized placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: UTIs are the most common outpatient infections with a lifetime incidence of 50–60% in adult women. D-Mannose has shown promise in trials based on secondary care, but effectiveness in placebo-controlled studies and community settings has not been established.

PATIENTS: Adult women with recurrent UTIs

INTERVENTION: D-mannose

CONTROL: Placebo

PRIMARY OUTCOME: UTIs

Secondary Outcome: Symptoms, time to next consultation for UTI, suspected UTIs, lab-proven UTIs, antibiotic prescriptions, hospital admissions for UTIs

METHODS (BRIEF DESCRIPTION):

- Patients were women ≥18 years old living in the UK and had evidence of recurrent UTIs as defined as outpatient UTI diagnosis and/or prescription for UTI-specific antibiotics ≥3 in the last year or ≥2 times in the last six months.
- Patients were masked and randomized to one of the following:
  - 2 g daily of D-mannose powder
  - 2 g daily of matched volume placebo fructose powder
- The primary outcome was the number of women who sought medical treatment for at least one clinically suspected UTI within six months of starting the intervention.
- Outcomes were assessed via primary care record review.
- Secondary outcomes included symptoms reported via symptom diaries, time to next consultation for UTI, number of suspected UTIs, number of lab-proven UTIs, antibiotic prescriptions, and hospital admissions related to UTIs.

INTERVENTION (# IN THE GROUP): 303

COMPARISON (# IN THE GROUP): 295

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- There was no difference in recurrent UTIs between D-mannose and fructose groups (51% vs 56%, respectively; risk difference –5.0%; 95% CI, –13% to 3%).

Secondary Outcome –

- There were no significant differences between the D-mannose group and the placebo group in symptom severity, time to next consultation, antibiotic prescriptions, and number of hospitalized patients related to UTIs.

LIMITATIONS:

- There was a possibility of underdosing. The use of capsules, as opposed to a serving spoon, may have improved dosing consistency.
- D-mannose and fructose are both sugars. There may have been a different outcome had they compared the results against a group that was untreated or used a true placebo.

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Safety of Weight Loss or Minimal Weight Gain During Pregnancy in Patients with Obese BMIs

Safety of Low Weight Gain or Weight Loss in Pregnancies with Class 1, 2, and 3 Obesity: A Population-Based Cohort Study

Johansson K, Bodnar LM, Stephansson O, Abrams B, Hutcheon JA. Safety of low weight gain or weight loss in pregnancies with class 1, 2, and 3 obesity: a population-based cohort study. *Lancet*. 2024;403(10435):1472-1481. doi:10.1016/S0140-6736(24)00255-1

KEY TAKEAWAY: In patients with body mass index (BMI) of 30–39.9 kg/m^2 gestational weight gain <5 kg or weight loss was not associated with adverse outcomes. Gestational weight gain <5 kg or weight loss was associated with a decrease in the risk of adverse outcomes in patients with BMI ≥40 kg/m^2.

STUDY DESIGN: Prospective observational cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: According to the 2009 US Institute of Medicine (IOM) guidelines, pregnant patients with obese BMIs should gain 5–9 kg of weight during pregnancy. Some previous studies have suggested that a smaller amount of weight gain may be appropriate for pregnant patients with obesity, but there is a lack of robust evidence comparing infant and maternal outcomes.

PATIENTS: Pregnant individuals with obese BMI

INTERVENTION: Gestational weight gain <5 kg

CONTROL: Gestational weight gain ≥5 kg

PRIMARY OUTCOME: Composite of adverse maternal or fetal outcomes

METHODS (BRIEF DESCRIPTION):

- Participants included patients from the Stockholm-Gotland Perinatal Cohort with singleton pregnancies between January 1, 2008, and December 31, 2015, with early pregnancy (<14 weeks gestation) BMI ≥30 kg/m^2.
- Patient BMI was calculated using first measured gestational weight at <14 weeks gestation and used to classify patients into obesity categories of class one (30.0–34.9 kg/m^2), class two (35.0-39.9 kg/m^2), or class three (≥40 kg/m^2).
- Patients without antenatal weight gain measurements, missing or implausible BMI during early pregnancy, or early pregnancy BMI <30 kg/m^2 were excluded from the study.
- The average age of participants was 32 years old for class one obese patients, 31 for class two obese patients, and 32 for class three obese patients.
- Total gestational weight gain was measured by subtracting early pregnancy weight from weight at or before delivery.
- Z scores were calculated for antepartum weight gain.
- A composite outcome was created including 10 adverse maternal or infant outcomes associated with gestational weight gain according to the IOM, weighted based on severity.
    - These included gestational diabetes, preeclampsia, unplanned cesarean delivery, new-onset longer-term maternal cardiometabolic disease after pregnancy, postpartum weight increase, stillbirth, infant death, preterm birth, small-for-gestational-age birth, and large-for-gestational-age birth.
- Poisson regression was used to plot z scores with composite outcomes.
- Rate ratios were calculated with 95 percent confidence intervals for each z score at 0.1 intervals –3 to 3, with –1.1 corresponding to 5 kg weight gain, or the lower limit of recommended weight gain during pregnancy per the IOM for individuals with obese BMI.

INTERVENTION (# IN THE GROUP): 2,719

COMPARISON (# IN THE GROUP): 13,041

FOLLOW-UP PERIOD: Median 7.9 years

RESULTS:

Primary Outcome –

- Gestational weight gain <5 kg or weight loss did not impact maternal and infant outcomes compared to ≥5 kg of weight gain in patients with class one obesity (rate ratio [RR] 0.97; 95% CI, 0.89–1.1) or class two obesity (RR 0.96; 95% CI, 0.86–11).
- Gestational weight gain <5 kg or weight loss decreased the risk of adverse maternal and infant outcomes compared to ≥5 kg of weight gain in patients with class three obesity (RR 0.81; 95% CI, 0.71–0.89).

LIMITATIONS:

- The majority of the population was women born in Nordic countries with publicly funded antenatal care, therefore limiting generalizability.
- Infant obesity and longer-term maternal obesity were not measured directly; large-for-gestational-age birth and interpregnancy weight increase were used to indirectly identify these outcomes.

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Move Over Aspirin: Is Clopidogrel the New Platelet Sheriff in Town Following PCI?

Aspirin Versus Clopidogrel for Long-Term Maintenance Monotherapy After Percutaneous Coronary Intervention: The HOST-EXAM Extended Study

Kang J, Park KW, Lee H, et al. Aspirin Versus Clopidogrel for Long-Term Maintenance Monotherapy After Percutaneous Coronary Intervention: The HOST-EXAM Extended Study. *Circulation*. 2023;147(2):108-117. doi:10.1161/CIRCULATIONAHA.122.062770

KEY TAKEAWAY: Following percutaneous coronary intervention (PCI) and 6–18 months of dual antiplatelet therapy (DAPT), clopidogrel monotherapy compared to aspirin significantly decreases the composite outcome of all-cause mortality, major cardiovascular events, and bleeding events.

STUDY DESIGN: Cohort study extension of an open-label RCT

LEVEL OF EVIDENCE: STEP 3 (downgraded due to open-label design and observational component)

BRIEF BACKGROUND INFORMATION: Lifelong, low-dose aspirin has been considered the standard of care for secondary prevention after PCI and initial treatment with DAPT for 6–12 months. However, this is based on studies from decades ago before the widespread use of statins or drug-eluting stents. The HOST-EXAM study found that clopidogrel monotherapy for two years led to a reduction in the primary composite endpoint of all-cause mortality, nonfatal myocardial infarction (MI), stroke, acute coronary syndrome (ACS) readmission, and major bleeding compared to aspirin monotherapy. This extended study sought to evaluate these outcomes beyond two years of monotherapy follow-up.

PATIENTS: Adults with prior PCI

INTERVENTION: Clopidogrel

CONTROL: Aspirin

PRIMARY OUTCOME: Composite of all-cause mortality, major cardiovascular event, bleeding event

Secondary Outcome: Any thrombotic or bleeding event

METHODS (BRIEF DESCRIPTION):

- The original HOST-EXAM study enrolled adults ≥20 years old from centers in Korea who received PCI with drug-eluting stent (DES) followed by DAPT for 6–18 months with no further clinical events and randomized them 1:1 to receive two years of either 100 mg aspirin or 75 mg clopidogrel.
- The extended study followed these same patients (prospective and retrospective cohorts) for a median of an additional 3.8 years for the same outcomes.
- Exclusion criteria: Active or history of bleed, known coagulopathy, need for intervention requiring a break from antiplatelets for >3 months, women breastfeeding or of child-bearing potential, or currently taking certain medications including anticoagulants, lithium, high-dose methotrexate, prasugrel or ticagrelor, or certain CYP2C19 inhibitors (including fluoxetine).
- At baseline participants had an average age of 63 years old, an average BMI of 25, 75% male, 61% with hypertension, 34% with diabetes, 21% smokers, 16% with previous MI, and 12% with chronic kidney disease (CKD).
- The primary outcome was a composite of all-cause mortality, non-fatal MI, stroke, ACS readmission, and major bleeding events defined as Bleeding Academic Research Consortium (BARC) type 3–5.
    - BARC 3–5 summarized as overt bleeding leading to hemoglobin drop >3, transfusion, or significant event including cardiac tamponade, surgical intervention, and fatality.
- Secondary outcomes: Thrombotic events (composite of cardiac death, non-fatal MI, ischemic stroke, ACS readmission, and definite or probable stent thrombosis), any bleed (BARC 2–5); and individual events (CV death, non-CV death, nonfatal MI, any stroke, ischemic stroke, hemorrhagic stroke, ACS readmission, major bleed [BARC 3–5], revascularizations, and stent thrombosis).

INTERVENTION (# IN THE GROUP): 2,431

COMPARISON (# IN THE GROUP): 2,286

FOLLOW-UP PERIOD: Median 3.8 years

RESULTS:

Primary Outcome –

- Clopidogrel was superior to aspirin in reducing the primary composite endpoint (13% vs 17%, respectively; hazard ratio [HR] 0.74; 95% CI, 0.63–0.86).

Secondary Outcome –

- Clopidogrel was superior to aspirin in reducing the thrombotic composite endpoint (8.1% vs 12%, respectively; HR 0.66; 95% CI, 0.55–0.79).
- Clopidogrel reduced any bleed compared to aspirin (4.5% vs 6.1%, respectively; HR 0.74; 95% CI, 0.57–0.94).
- Clopidogrel reduced any stroke (ischemic and hemorrhagic) compared to aspirin (1.5% vs 2.9%, respectively; HR 0.53; 95% CI, 0.35–0.79).
- Clopidogrel reduced ACS readmissions compared to aspirin (4.6% vs 7.7%, respectively; HR 0.59; 95% CI, 0.47–0.75).
- Clopidogrel reduced major bleeding compared to aspirin (2.6% vs 3.9%, respectively; HR 0.65; 95% CI, 0.47–0.90).
- Clopidogrel reduced any revascularization compared to aspirin (5.3% vs 6.9%, respectively; HR 0.77; 95% CI, 0.61–0.98).
- There was no statistically significant difference in all-cause mortality, cardiovascular death, non-cardiovascular death, non-fatal MI, or stent thrombosis.

LIMITATIONS:

- The study population was limited to Korean people and may not be generalizable to other ethnicities.
- Women were underrepresented in the trial, accounting for only about 25% of the study population, which also limits generalizability.
- The use of 100 mg aspirin in the control group instead of 81 mg more commonly used in the US may have impacted bleeding events.
- Between the end of the initial study and the beginning of the extended study, 583 patients were excluded from analysis because their antiplatelet regimen was changed, most often due to “physician clinical decision”, which was the reason for the switch 66% of the time and may have introduced bias.
- Studies beyond five years of follow-up are needed because antiplatelet monotherapy is recommended for life.
- The open-label design potentially introduced reporting bias.
- There was possible selection bias or under-reported events because the primary endpoint occurred significantly less than expected based on sample size.

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No CAP: The Inappropriate Diagnosis of Pneumonia Can Harm Patients

Inappropriate Diagnosis of Pneumonia Among Hospitalized Adults

Gupta AB, Flanders SA, Petty LA, et al. Inappropriate Diagnosis of Pneumonia Among Hospitalized Adults. *JAMA Intern Med*. 2024;184(5):548-556. doi:10.1001/jamainternmed.2024.0077

KEY TAKEAWAY: Inappropriate diagnosis of community-acquired pneumonia (CAP) was relatively common across 48 Michigan hospitals. Patients are more likely to be inappropriately diagnosed with CAP if they have an altered mental status or a history of dementia.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Harms associated with inappropriate CAP diagnoses may include delayed identification and management of alternative pathologies, adverse effects of antibiotics, and development of antibiotic resistance. Despite the impact of inappropriate diagnoses on patients and healthcare systems, the frequency and associated harms of CAP misdiagnosis in hospitalized patients are not well understood.

PATIENTS: Patients hospitalized for treatment of pneumonia

INTERVENTION: Not applicable

CONTROL: Not applicable

PRIMARY OUTCOME: Percentage of patients inappropriately diagnosed with CAP, antibiotic treatment, adverse events

METHODS (BRIEF DESCRIPTION):

- Patients hospitalized in 48 Michigan hospitals over three years were retrospectively included in the study if they were discharged with a CAP diagnosis and received antibiotics on days one or two of admission.
- The study population had a mean age of 70 years old, 50% female, 50% male, 21% Black, 76% White, and 3.5% other.
- Exclusion criteria included treatment for an additional infection unrelated to pneumonia, severely immunocompromised status, pregnancy, admission for comfort measures, who left against medical advice (AMA), intensive care unit (ICU) stay, ventilator use during hospitalization, admission to hospitals with >10 qualifying patients, missing or unknown antibiotic data, received >14 days antibiotic treatment, or had documented COPD exacerbation treated with azithromycin or doxycycline.
- Inappropriate diagnosis was determined with National Quality Forum-endorsed criteria of <2 signs or symptoms of pneumonia or lack of radiographic findings consistent with pneumonia.

INTERVENTION (# IN THE GROUP): 17,290

COMPARISON (# IN THE GROUP): Not applicable

FOLLOW-UP PERIOD: Hospital admission to 30-days post-discharge

RESULTS:

Primary Outcome –

- Of the 17,290 patients included in the study for inpatient treatment of CAP, 2,079 (12%) were inappropriately diagnosed.
- In the adjusted analysis, several factors were associated with an increased risk of inappropriate CAP diagnosis, including:
  - Altered mental status (adjusted odds ratio [aOR] 1.8; 95% CI, 1.6–2.1)
  - History of dementia (aOR 1.8; 1.6–2.1)
  - Older adults (aOR 1.1; 95% CI, 1.1–1.1 per decade)
- 88% of patients inappropriately diagnosed with CAP were treated with full course antibiotics (>3 days) with a median of seven (5–9) days of antibiotics administered.
- The composite outcome of 30-day post-discharge adverse events occurred in 26% of patients who received an inappropriate CAP diagnosis.

LIMITATIONS:

- Determining accurate diagnoses from medical records can be flawed by inherent inaccuracies or omissions from the record (misclassification).
- Underestimation of inappropriate diagnosis of CAP may have biased toward the null.
- Antibiotic-related harms within the post-discharge period may be poorly estimated due to poor documentation or poor attention to antibiotic-related adverse events.

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Screens and Dreams: Sleep Worsens with Non-Productive Screen Time

When and What: A Longitudinal Study on the Role of Screen Time and Activities in Adolescent Sleep

Chen Y, Li Y, Li S, et al. When and what: A longitudinal study on the role of screen time and activities in adolescent sleep. *Sleep Med.* 2024;117:33-39. doi:10.1016/j.sleep.2024.03.008

KEY TAKEAWAY: Increased daytime screen, nighttime music, and social media use are associated with worse sleep outcomes. Screen time related to online shopping, working, and studying have a small association with improved sleep outcomes.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Electronic devices are used by nearly all adolescents, and the effect on sleep has been a concern for many. There has not been enough research to elucidate the relationship between screen time and sleep outcomes. This study sought to identify if greater screen time and types of screen time were associated with changes in sleep outcomes.

PATIENTS: Healthy adolescents

INTERVENTION: More screen time

CONTROL: Less screen time

PRIMARY OUTCOME: Sleep quality, excessive daytime sleepiness, insomnia

METHODS (BRIEF DESCRIPTION):

- Chinese adolescents 14–19 years old in secondary school students with no reported health complaints completed online surveys via the Wenjuanxing platform (N=831).
- Three surveys were distributed at the start of the study, then at three months, and the final at six months.
- Screen time was self-reported in hours per day, night, and during various periods. Such as:
  - "How much time (in hours) a day do you normally use electronic screens between 7 PM and bedtime"
- The activities during screentime were self-reported in hours.
- The first survey was before the COVID-19 pandemic and the second and third surveys took place during lockdown.
- Sleep quality was measured by the Pittsburgh Sleep Quality Index (PSQI) with 18 self-reported items with a max score of 21. Scores >5 indicate poor sleep while ≤4 indicates good sleep.
- Excessive Daytime Sleepiness was measured by the Epworth Sleepiness Scale (ESS) which uses eight self-reported items on a four-point Likert scale with a max score of 24. There was no indication which cut-off was used. Typically, ≥10 indicates excessive daytime sleepiness.
- Insomnia symptoms were measured by the Insomnia Severity Index (ISI). A five-question survey with a four-point Likert scale. Scores of 0–7 indicate no clinically significant insomnia, 8–14 indicate mild insomnia, 15–21 indicate moderate insomnia and 22–28 indicate severe insomnia.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Six months

RESULTS:

Primary Outcome –

- Daytime screen time with TV was associated with worse sleep quality (β 0.05, *P*=.008).
- Social media use was associated with worse sleep quality (β 0.04, *P*=.04).
- Nighttime music listening was associated with worse sleep quality (β 0.04, *P*=.02).
- Working and studying screen time was associated with improved sleep quality (β –0.05, *P*=.02).
- Increased online shopping screen time was associated with improved sleep quality (β –0.05, *P*=.01).
- Nighttime music listening was associated with worse daytime sleepiness (β 0.05, *P*=.01).
- Daytime screen time with TV was associated with worse insomnia (β 0.05, *P*=.001).
- Working and studying screen time was associated with improved insomnia (β –0.04, *P*=.04).

LIMITATIONS:

- COVID-19 quarantine began between wave one and two of the study.
- The population was Chinese students which may or may not be attributable to youth in other areas.

- All participants had no self-reported mental/physical health problems.
- Participants who did not complete the second and third surveys were not included in the analysis.
- The results do not indicate causality, only association.
- There may be confounding factors such as unrecognized mental illness, environmental factors such as lightning and noise, and social and emotional factors.

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The Interconnection of Sleep, Interactive Device Use, and Mental Health

Adolescents' Interactive Electronic Device Use, Sleep and Mental Health: A Systematic Review of Prospective Studies

Dibben GO, Martin A, Shore CB, et al. Adolescents' interactive electronic device use, sleep and mental health: a systematic review of prospective studies. *J Sleep Res.* 2023;32(5):e13899. doi:10.1111/jsr.13899

KEY TAKEAWAY: Interactive electronic device (IED) use may be associated with sleep quality and mental health, but additional investigation is required to determine an association.

STUDY DESIGN: Systematic review of 28 qualitative studies including 19 longitudinal cohort studies, one comparative analysis, two cross-sectional, three single-arm pre-post interventional, and one laboratory study (N = not provided).

LEVEL OF EVIDENCE: STEP 4 (downgraded due to high heterogeneity and high risk of bias).

BRIEF BACKGROUND INFORMATION: Current evidence regarding personal electronic device use and the impact it has on sleep quality and mental health among adolescents is minimal. There have been a handful of studies that suggest "adverse use", overuse, cyberbullying, peer pressure, and social media have been correlated with decreased mental health in adolescents. Additionally, publications have commented on sleep being the most impactful factor on mental health in the adolescent community. This study investigated the association between sleep, electronic device use, and mental health.

PATIENTS: Adolescents 10–19 years old

INTERVENTION: Interactive electronic device use

CONTROL: Not applicable

PRIMARY OUTCOME: Sleep and mental health outcomes

METHODS (BRIEF DESCRIPTION):

- Youths 10–24 years old without a mental illness or in an at-risk group were included in the study.
  - Most participants were in high-income countries.
- Studies not written in English were excluded.
- Device use was defined as "any type of interactive electronic device used at any time of day."
- The analysis included comparing use, time of certain sites, brightness, interactions with others, and adverse implications.
- Qualitative narration on observations was provided.
  - Quantitative synthesis was not performed given the profuse heterogeneity of studies.

INTERVENTION (# IN THE GROUP): Not available

COMPARISON (# IN THE GROUP): Not available

FOLLOW-UP PERIOD: Varied (1 day to 6 years)

RESULTS:

Primary Outcome –

- IED use and its impact on sleep was unclear (6 trials, n=2,006).
  - 14% of individual outcomes showed a negative association between IED use and sleep.
  - The remaining had no association.
- No consistent association was seen between length of IED use and quality of sleep (3 studies, n=63).
- The association between social media usage and IED on sleep quality was inconsistent, but the largest comparison completed demonstrated a negative association (33 trials, n=3,014).
  - One study suggested a positive relationship between Twitter and sleep quality, and the remaining showed no association (24 trials).
- Strict "lights out" for IED use may improve the time onset to sleep (n=569).
  - Comparatively, the quality of sleep and the feelings of rejuvenation had no association (n=26,205).
- IED-imposed cyberbullying and peer pressure consistently demonstrated a negative impact on sleep outcomes in 75% of studies (9 studies, n=45,220).
- Poor mental health and increased IED use were associated with worse sleep habits in 53% of the sample group (3 studies, n=14,841).

LIMITATIONS:

- High heterogeneity among studies in all areas (methods, results, measuring outcomes) resulted in the meta-analysis not being performed.
- Included studies had a high risk of bias.
- Language bias, only English-published studies.

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Bad Food, Bad Thoughts: Consumption of Ultra-Processed Foods and Adverse Mental Health Outcomes

Cross-Sectional Examination of Ultra-Processed Food Consumption and Adverse Mental Health Symptoms

Hecht EM, Rabil A, Martinez Steele E, et al. Cross-sectional examination of ultra-processed food consumption and adverse mental health symptoms. *Public Health Nutr.* 2022;25(11):3225-3234. doi:10.1017/S1368980022001586

KEY TAKEAWAY: Individuals with the highest level of ultra-processed foods (UPF) consumption (>80%) were significantly more likely to report at least mild depression, more mentally unhealthy days, and more anxiety per month compared to a reference UPF intake of 0–19%.

STUDY DESIGN: Cross-sectional

LEVEL OF EVIDENCE: STEP 4 (downgraded due to possible recall bias and confounding factors)

BRIEF BACKGROUND INFORMATION: Ultra-processed foods (UPF) make up a large portion of the American diet, but these foods have depleted nutritional value and increased sugars, saturated fats, and salt. Previous studies have shown that consuming UPF is associated with depression, but there is no clear data on the connection between anxiety and other mental health concerns. The study aimed to compare the consumption of varying levels of processed foods to different mental health outcomes.

PATIENTS: US adults >18 years old

INTERVENTION: High UPF exposure

CONTROL: Low UPF exposure

PRIMARY OUTCOME: Depression, mentally unhealthy days, and anxiety

METHODS (BRIEF DESCRIPTION):

- Adults who had both dietary data and information regarding depression, mentally unhealthy days, and anxiety within the National Health and Nutrition Examination Survey (NHANES) were included.
- Individuals who had current/past use of cocaine, methamphetamine, and heroin use were excluded from the study.
- Groups were separated based on the exposure to ultra-processed foods compared to the reference range of 0–19%.
    - Ranges included 20–39%, 40–59%, 60–79%, and >80%.
- Primary outcomes were measured based on depression, mentally unhealthy days, and anxiety with the following adjusted criteria: Age, gender, race/ethnicity, BMI, smoking status, and physical activity.
    - Depression was monitored with PHQ9 scores with mild depression as the cutoff with a PHQ9 score of >5.
    - Mental health days with the question "During the past 30 days, how many days was your mental health not good?" with a range of 1–30 days.
    - Anxiety was measured with the question "During the past 30 days, how many days did you feel worried, tense, or anxious?"

INTERVENTION (# IN THE GROUP):

- 20–39%: 1,860
- 40–59%: 4,023
- 60–79%: 3,286
- >80%: 885

COMPARISON (# IN THE GROUP): 0–19%: 305

FOLLOW-UP PERIOD: Not applicable

RESULTS:

Primary Outcome –

- Higher UPF exposure was associated with mild depression more than lower UPF exposure (odds ratio [OR] 1.8; 95% CI, 1.1–3.0).
- Higher UPF exposure was associated with more mentally unhealthy days than lower UPF exposure (risk ratio [RR] 1.2; 95% CI, 1.2–1.3).
- Higher UPF exposure was associated with more anxious days than lower UPF exposure (RR 1.2; 95% CI, 1.2–1.2).
- As the level of UPF increased, the risk ratio for depression, mentally unhealthy days, and anxious days significantly increased. This is evidenced by the lowest UPF consumption (20–39%) outside of the reference (0–19%) having an adjusted risk ratio of 0.95 when compared to the highest consumption (>80%) at 1.2.

LIMITATIONS:

- The data was based on self-reporting opening the study up to recall bias and individuals misclassifying data.
- NHANES may not have the most accurate data on the processing of foods.
- Due to social determinants of health, confounding other lifestyle risks may be present as well.
- No definition for “mentally unhealthy” or “anxious” days was given.

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