GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

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SPOTLIGHT: Acetazolamide May Now Make Traveling to High Altitudes a Possibility, Even for Those with COPD

- Efficacy of Hybrid vs High-Dose Dual vs Bismuth Quadruple Therapies for *H. pylori* in Taiwan
- Do Diagnostic Errors Cause Real World Harm in Hospital Patients?
- Improving Attention in Children: Have You Tried Playing Video Games?

Acetazolamide May Now Make Traveling to High Altitudes a Possibility, Even for Those with COPD

Acetazolamide to Prevent Adverse Altitude Effects in COPD and Healthy Adults

Furian M, Mademilov M, Buergin A, et al. Acetazolamide to Prevent Adverse Altitude Effects in COPD and Healthy Adults. *NEJM Evid*. 2022;1(1):EVIDoa2100006. doi:10.1056/EVIDoa2100006

KEY TAKEAWAY: Acetazolamide prevents adverse altitude effects in patients with chronic obstructive pulmonary disease (COPD) and healthy adults.

STUDY DESIGN: Randomized, placebo-controlled, double-blind, parallel-group trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Patients with COPD are more susceptible to altitude-related adverse health effects (ARAHE). Acetazolamide has been shown to improve oxygenation when taken at high altitudes, however, its effects in individuals over 40 years old have not been reported.

PATIENTS: Patients with COPD and healthy individuals

INTERVENTION: Acetazolamide

CONTROL: Matching placebo

PRIMARY OUTCOME: ARAHE and acute mountain sickness (AMS)

Secondary Outcome: Nocturnal oxygenation, subjective sleep quality, blood pressure, adverse events

METHODS (BRIEF DESCRIPTION):

- The study consisted of two trials:
  - Trial one included men and women 18–75 years old, living at a location no more than 800 m above sea level, diagnosed with COPD.
  - Trial two included healthy individuals, 40–75 years old, residing in an area no more than 800 m above sea level.
- Participants stayed for two days and nights in a high-altitude clinic at 3100 m. Capsules were administered 24 hours before and during the stay.
- Patients were blinded and randomized to one of the following treatments:
  - Acetazolamide (125 mg, 1 in the morning and 2 in the evening)
  - Identical-looking placebo capsules
- The primary outcome was measured as the incidence of ARAHRE and AMS.
  - AMS was evaluated using the Lake Louise questionnaire score (LLS) and the cerebral component of the Environmental Symptoms Questionnaire.
    - The LLS measured self-assessed symptoms with scores ranging from 0–15 points (absent to severe).
    - The score on the Environmental Symptoms Questionnaire reflected AMS. AMSc; the scale of self-assessed symptoms ranges from 0–5 points (no symptoms to extreme).
  - A LLS sum score of ≥3 including headache or an AMSc score of ≥0.7 were assumed to indicate the presence of AMS.
- The secondary outcomes were measured as:
  - Clinical examination (weight, heart rate, pulse oximetry and mean arterial blood pressure)
  - Arterial blood gas exchange
  - Spirometry
  - Respiratory sleep studies that included nocturnal SpO_2, time spent with SpO_2 <85%, Oxygen desaturation index >3% dips/hr, and sleep quality.
  - Participants rated treatment-related side effects on a 4-point Likert scale ranging from 0–3 points (absent to severe).
  - Participants used a visual analog scale ranging from 0–100 mm (extremely bad to excellent) to score the quality of their sleep in the morning.

INTERVENTION (# IN THE GROUP):

- Individuals with COPD: 86
- Individuals without COPD: 175

COMPARISON (# IN THE GROUP):

- Individuals with COPD: 90
- Individuals without COPD: 170

FOLLOW-UP PERIOD: Two days

RESULTS:

Primary Outcome –

- In participants with COPD, acetazolamide improved the incidence of ARAHE compared to placebo (hazard ratio [HR] 0.54; 95% CI, 0.37–0.79).
- In participants with COPD, acetazolamide improved the incidence of AMS compared to placebo (HR 0.80; 95% CI, 0.45–1.4).

- In participants without COPD, acetazolamide improved the incidence of ARAHE compared to placebo (HR 0.42; 95% CI, 0.29–0.61).
- In participants without COPD, acetazolamide improved the incidence of AMS compared to placebo (HR 0.48; 95% CI, 0.29–0.80).

Secondary Outcome –

- In participants with COPD, acetazolamide resulted in the following compared to placebo:
  - Less of a drop in oxygen saturation (between-group difference –23%; 95% CI, –31 to –14)
  - Reduced altitude-related nocturnal hypoxemia (between-group difference 1.7%; 95% CI, 0.9–2.5)
  - Better subjective sleep quality (between-group difference 13 mm; 95% CI, 2–23)
  - Less of an increase in blood pressure (between-group difference –7 mmHg; 95% CI, –11 to –3)
- Among the participants with COPD, 21% of patients in the placebo group and 28% in the acetazolamide group experienced paresthesia.
- In participants without COPD, acetazolamide resulted in the following compared to placebo:
  - Reduced altitude-induced nocturnal hypoxemia (between-group difference 3.2%; 95% CI, 2.5–3.9)
  - Reduced sleep apnea (between-group difference –9.2%; 95% CI, –12 to –6.5)
  - Decrease in blood pressure rise (between-group difference –5 mmHg; 95% CI, –8 to –3)
  - Improved subjective sleep quality (between-group difference 9 mm; 95% CI, 2–16)
- Among the participants without COPD, 42% of patients in the placebo group and 59% in the acetazolamide group experienced paresthesia.

LIMITATIONS:

- Comparisons of primary outcomes between the two trials were not possible due to safety precautions (severe hypoxemia; SpO_2 of <80% for >30 minutes or <75% for >15 minutes) was included in the ARAHE composite primary endpoint that resulted in the withdrawal of participants in COPD group.
- Incomplete assessment of secondary outcomes in a group with COPD patients due to ARAHE-related dropout.

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Efficacy of Hybrid vs High-Dose Dual vs Bismuth Quadruple Therapies for *H.pylori* in Taiwan

Hybrid, High-Dose Dual and Bismuth Quadruple Therapies for First-Line Treatment of Helicobacter Pylori Infection in Taiwan: A Multicenter, Open-Label, Randomized Trial

Hsu PI, Chen KY, Tai WC, et al. Hybrid, High-Dose Dual and Bismuth Quadruple Therapies for First-Line Treatment of Helicobacter pylori Infection in Taiwan: A Multicenter, Open-Label, Randomized Trial. *Am J Gastroenterol.* 2023;118(7):1184-1195. doi:10.14309/ajg.0000000000002255

KEY TAKEAWAY: In *H. pylori* treatment, 14-day hybrid therapy (HT) and 10-day bismuth quadruple therapy (BQT) are more effective than 14-day high-dose dual therapy (HDDT). Hybrid BQT shows more side effects than high-dose dual therapies.

STUDY DESIGN: Multicenter, open-label, randomized trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The American College of Gastroenterology recommends BQT as first-line therapy for *H. pylori,* but there are reported adverse events and complexity with its usage.

PATIENTS: Patients with *H. pylori* infection

INTERVENTION: 14-day HT or 14-day HDDT

CONTROL: 10-day BQT

PRIMARY OUTCOME: Eradication of *H. pylori* infection

Secondary Outcome: Adverse events, medication adherence

METHODS (BRIEF DESCRIPTION):

- Participants were from nine centers in Taiwan.
  - Included participants: ≥20 years old who had undergone EGD to investigate GI symptoms, were invited to an *H. pylori* screening program, and had either positive rapid urease and histology or positive culture.
  - Excluded participants: Previous eradication treatment for *H. pylori*, previous allergic reactions to study medications, history of gastrectomy, used antibiotics in the last four weeks, pregnant/lactating women, or coexistence of serious concomitant disease.
- Eligible participants were randomly allocated 1:1:1 using permuted block randomization into:
  - 14-day HT consisted of rabeprazole 20 mg and amoxicillin 1 g BID for seven days, followed by rabeprazole 20 mg, amoxicillin 1 g, clarithromycin 500 mg, and metronidazole 500 mg BID for seven days.
  - 14-day HDDT consisted of rabeprazole 20 mg and amoxicillin 750 mg four times daily for 14 days.
  - 10-day BQT consisted of rabeprazole 20 mg BID, tripotassium dicitrato bismuthate 300 mg four times daily, tetracycline 500 mg four times daily, and metronidazole 250 mg four times daily.
- Anti-*H. Pylori* drugs were taken 30 minutes before meals, alcohol was prohibited.
- Adherence was assessed after two weeks and *H. pylori* status at least four weeks after treatment completion and two weeks free of PPI/H_2 receptor antagonist usage with a ^{13}C-urea breath test.
- Adverse events were measured using a four-point scale, and drug adherence was assessed by pill counts.

INTERVENTION (# IN THE GROUP):

- HT: 306
- HDDT: 306

COMPARISON (# IN THE GROUP): 306

FOLLOW-UP PERIOD: Four weeks after completion of treatment

RESULTS:

Primary Outcome –

- 14-day HT and 10-day BQT were both superior compared to 14-day HDDT:
  - 14-day HT (difference 8.2%; 95% CI, 4.5–12%)
  - 10-day BQT (difference 6.9%; 95% CI, 1.6–12%)

Secondary Outcome –

- 14-day HDDT demonstrated fewer adverse events than 14-day HT and 10-day BQT (13% vs 27% and 32%, respectively; *P*<.001).
- Drug adherence was better in patients treated with 14-day HDDT and those treated with 14-day than those treated with 10-day BQT (98% and 98% vs 94%, respectively; *P*=.005).

LIMITATIONS:

- Investigators were blind to treatment allocation. Patients were aware of their treatment and no group was given a placebo.
- Higher levels of amoxicillin resistance existed in the HDDT group compared to the HT group.
- A higher frequency of metronidazole resistance existed in the HDDT group relative to the BQT group.
- 4% of eligible patients (33) were lost to follow-up and were counted as eradication failure.

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Do Diagnostic Errors Cause Real World Harm in Hospital Patients?

Diagnostic Errors in Hospitalized Adults Who Died or Were Transferred to Intensive Care

Auerbach AD, Lee TM, Hubbard CC, et al. Diagnostic Errors in Hospitalized Adults Who Died or Were Transferred to Intensive Care. *JAMA Intern Med.* 2024;184(2):164-173. doi:10.1001/jamainternmed.2023.7347

KEY TAKEAWAY: Nearly a quarter of patients who were admitted to the intensive care unit (ICU) or who died during their stay, experience a diagnostic error and this diagnostic error may contribute to the death of 6.6% of patients.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: There is limited research on the incidence of diagnostic errors and the harm they cause to patients during their hospital stay. Errors are known to contribute to adverse events, but most studies currently look at specific types of errors and thus undercount events. Through a systematic approach, the authors set out to capture error types and the harm they cause.

PATIENTS: Hospitalized adults

INTERVENTION: Presence of diagnostic error

CONTROL: No diagnostic error

PRIMARY OUTCOME: Harm due to diagnostic error

METHODS (BRIEF DESCRIPTION):

- Researchers screened charts from 29 hospitals in the United States to identify patients who were admitted with a general medication condition and either died or were transferred to the ICU after two days of hospitalization in 2019.
- Up to 100 charts from each hospital were randomly selected for further review.
- A total of 2,428 charts (mean age 64 years old, 45.6% female) were reviewed by groups of 2–3 trained physicians using the Safer-Dx algorithm to determine if a diagnostic error occurred during a patient stay.
- There was a quality assurance process to review outliers.
- Charts were also reviewed using an adapted Diagnostic Error Evaluation and Research (DEER) framework to determine if a process fault occurred and if that fault led to harm.
- The DEER framework looks at where in the diagnostic process error may have occurred, including access, history, physical exam, tests, assessments, referral/consultations, and follow-up.
- Patient groups (error present or absent) were compared for confounding variables.
- Harms prevalence severity was measured using the National Coordinating Council for Medication Error Reporting and Prevention scale.
- DEER process fault prevalence and error attribution were calculated using multivariable models.

INTERVENTION (# IN THE GROUP): 550

COMPARISON (# IN THE GROUP): 1,878

FOLLOW-UP PERIOD: Duration of hospital stay

RESULTS:

Primary Outcome –

- The mean error rate was 23% (standard deviation [SD] 42%). Of those, 77% (95% CI, 72–82) with an error experienced harm.
- A total of 6% (95% CI, 5.3–8.2) of all patients reviewed had errors contribute to their death and 23% (95% CI, 19–28) of all patients with errors died.
- Significantly important patient characteristics leading to error included:
  - Patient/caregiver preference: (11% error present vs 16% error absent; *P*=.003)
  - Housing instability: (5.3% error present vs 2.5% error absent; *P*=.001)
  - Altered mental status on admission (41% error present vs 48% error absent; *P*=.003)
  - Any other barriers to communication (32% error present vs 39% error absent; *P*=.002)
- Process faults were found in all DEER areas, process faults in:
  - Testing: (adjusted attributable fractions [aAF] 20; 95% CI, 15–25)
  - Assessment: (aAF 21; 95% CI, 16–26) which had the highest risk for causing a diagnostic error

LIMITATIONS:

- Collection and sample bias reduced generalization because the study was done at a collection of

academic medical centers and only evaluated patients who deteriorated or died during the stay.

- This study only looked at the prevalence of harm and does not provide meaningful data to help clinicians reduce harm to patients.
- Physician work environment (census, culture, etc) was unable to be measured.

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Improving Attention in Children: Have You Tried Playing Video Games?

Electrophysical Brain Changes Associated with Cognitive Improvement in a Pediatric Attention Deficit Hyperactivity Disorder Digital Artificial Intelligence-Driven Intervention: Randomized Controlled Trial

Medina R, Bouhaben J, de Ramón I, et al. Electrophysiological Brain Changes Associated with Cognitive Improvement in a Pediatric Attention Deficit Hyperactivity Disorder Digital Artificial Intelligence-Driven Intervention: Randomized Controlled Trial. *J Med Internet Res*. 2021;23(11):e25466. Published 2021 Nov 26. doi:10.2196/25466

KEY TAKEAWAY: It is not clear if artificial intelligence (AI) driven digital interventions can reduce attention deficit hyperactivity disorder (ADHD) symptoms in pediatric patients.

STUDY DESIGN: Single-center, parallel, single-blind, randomized controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to high rate of dropout)

BRIEF BACKGROUND INFORMATION: Video games require players to engage in sustained attention, response inhibition, and utilize functional working memory to complete objectives. If these could be tailored to a patient's needs, video games could be used as a therapy to help with executive function dysregulation for children with ADHD. AI could help identify where these deficits occur and augment play to strengthen these skills.

PATIENTS: Children with ADHD

INTERVENTION: AI-driven video game

CONTROL: Other video games

PRIMARY OUTCOME: Improvement in ADHD symptoms
Secondary Outcome: Magnetoencephalographic (MEG) findings

METHODS (BRIEF DESCRIPTION):

- This study was designed to be a proof of concept for digital interventions and treatment of ADHD in children.
- Pediatric patients 8–11 years old, diagnosed with ADHD-C by accredited experts following the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition.
- Participants were required to stop ADHD medications three days before assessment and intervention and continue this for the duration of the study.
- The experimental group had an average age of 9.2 years old, 45% were male, 31% were on medication before the study, and 13% received psychological treatment before the study.
- The control group had an average age of 9.7 years old, 41% were male, 11% were on medication before the study, and 10% received psychological treatment before the study.
- The intervention group played an AI-driven video game.
- The control group played other commercial video games.
- Both groups played video games at home for 15–20 minutes three times a week for 12 weeks.
- Pre-intervention and post-intervention assessments were measured using MEG, ADHD screening tools, and the Conner's Continuous Performance Test, 3rd Edition (CPT-III).
- Conner's CPT-III assessed participants age eight years old and older, in four dimensions of attention: Inattentiveness, impulsivity, sustained attention, and vigilance.
- Higher commission error rate scores (near 70) were indicative of inattentiveness or impulsivity while lower scores (near 40) indicate less inattentiveness or impulsivity.
- MEG is a form of functional neuroimaging that identifies areas of electrical activity in the brain.
    - Areas of activity were noted in pre and post-intervention scans, results were filtered by identifying areas that experienced a change between .01–330 Hz.

INTERVENTION (# IN THE GROUP): 22

COMPARISON (# IN THE GROUP): 18

FOLLOW-UP PERIOD: 12 weeks

RESULTS:

Primary Outcome –

- There was no significant differences between the experimental and control groups (t_{27}=1.72; *P*=0.10) in the pre-intervention CPT-III score.

- There was no statistically significant difference between the two treatment groups post-intervention CPT-III scores.

Secondary Outcome –

- Correlation between CPT-III scores and power ratios between 11.67-13.33 Hz on MEG scans was shown to be significant in the intervention group (p=-0.0783; P=.004) but not for the control (p=-0.358; P=.2), suggesting that the changes in response inhibition, attention, and working memory were a result of the study's intervention.

LIMITATIONS:

- As a proof of concept trial, the small sample size with few females does not allow for generalization.
- This study would be difficult to replicate due to the use of proprietary AI-driven video gaming technology.
- High drop-out rate of 28%.
- The sample size estimate was not reliable.

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