GEMs
GOOD EVIDENCE MATTERS

GEMs of the Week

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What's in this week's issue?

Week of December 13 - 17, 2021

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- A Shot in the Dark? Ultrasound-Guided vs Blind Steroid Injections

Is Treating Inpatient Hypertension Beneficial?

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Treatment and Outcomes of Inpatient Hypertension Among Adults with Noncardiac Admissions

Radhika R, Sheehan MM, Hu B, Shaker V, Kojima L, Rothberg M. Treatment and Outcomes of Inpatient Hypertension Among Adults with Noncardiac Admissions. *JAMA Intern Med*. 2021; 181(3):345–352.

KEY TAKEAWAY: When patients were treated for inpatient hypertension in the absence of end-organ damage, outcomes were worse.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: Treating hypertension in an outpatient setting reduces adverse outcomes, but evidence for treating hypertension in an inpatient setting is lacking. Elevated blood pressures commonly occur in hospitalized patients, but it is unknown if treating inpatient hypertension improves patient outcomes.

PATIENTS: Adults hospitalized for noncardiac reasons

INTERVENTION: Intravenous (IV) antihypertensive or a new class of oral antihypertensive

CONTROL: No intervention or continuing current antihypertensive medications

OUTCOME: Inpatient stroke, myocardial infarction (MI), and acute kidney injury (AKI) individually and a composite of all three

Secondary Outcomes: Stroke and MI at 30 days, blood pressure (BP) at one year

METHODS (BRIEF DESCRIPTION):

- Included patients were ≥18 years old (mean 66 years old) and were admitted for noncardiac reasons.
- Patients were excluded if admitted for cardiovascular diagnosis in last 30 days, pregnant, or the length of stay <2 days or >14 days.
- Blood pressures from all patients were collected.
- Hypertension was defined as any systolic BP (SBP) ≥140 mmHg.
- The treatment group received either IV or a new class or oral antihypertensive for any SBP ≥140 mmHg.
- The control group received no treatment for any SBP ≥140 mmHg.
- Home medications for hypertension were continued.
- When determining outcomes, the index SBP for the treatment group was the highest treated SBP and for the untreated group the highest SBP was during admission.
- Outcomes 30 days after discharge compared those with medication intensification to those without. Intensification was defined as the prescription of an antihypertensive at the time of discharge that was not present preadmission.

INTERVENTION (# IN THE GROUP): 5,904

COMPARISON (# IN THE GROUP): 11,917

FOLLOW UP PERIOD: 30 days for incidence of stroke, AKI, and MI; one year for blood pressure control

RESULTS:

Primary Outcomes –

- Treatment for inpatient hypertension increased the risk of adverse events compared to no treatment. This was observed whether IV or oral antihypertensives were used and regardless of the magnitude of blood pressure elevation.
  - Composite of AKI, MI, and stroke: 11% vs 8.2% (odds ratio [OR] 1.4; 95% CI, 1.3–1.6)
  - AKI: 10% vs 7.9% (OR 1.4; 95% CI, 1.2–1.5)
    - This association was not significant when SBP was greater than 200 mmHg (OR 1.3; 95% CI, 0.63–2.9).
  - MI: 1.3% vs 0.6% (OR 2.2; 95% CI, 1.6–3.2)
  - Stroke outcomes alone were rare and not significantly different.

Secondary Outcomes –

- Medication intensification did not affect any of the following outcomes:
  - MI: 0.1% vs 0.2%; *P*>.99
  - Stroke: 0.5% vs 0.4%; *P*>.99
  - Blood pressure control: Average change –2.5 vs 2.3 mmHg; *P*=.83

LIMITATIONS:

- Dose intensification of current regimen was not considered treatment of hypertension.
- Patients with atrial fibrillation and congestive heart failure were included in the study.

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Esketamine Nasal Spray as Treatment for Active Suicidal Ideation

Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients with Major Depressive Disorder Who Have Active Suicide Ideation with Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II)

Ionescu DF, Fu DJ, Qiu X, et al. Esketamine Nasal Spray for Rapid Reduction of Depressive Symptoms in Patients with Major Depressive Disorder Who Have Active Suicide Ideation With Intent: Results of a Phase 3, Double-Blind, Randomized Study (ASPIRE II). *Int J Neuropsychopharmacol*. 2021; 24(1):22–31. doi:10.1093/ijnp/pyaa068

KEY TAKEAWAY: Esketamine nasal spray effectively decreases depression severity for patients with Major Depressive Disorder. However, remission rates are not significantly improved long-term.

STUDY DESIGN: Multicenter, multi-national, phase III, double-blind, randomized, placebo-controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Major Depressive Disorder (MDD) with suicidal ideation is managed with inpatient hospitalization and standard-of-care oral anti-depressant medications. Currently, there is no wildly used, fast-acting treatment for this patient population. Esketamine nasal spray was FDA approved for treatment-resistant depression in 2019.

PATIENTS: Adults 18–64 years old meeting DSM-5 criteria for MDD presenting with suicidal ideation

INTERVENTION: Esketamine 56–84 mg intranasal spray

CONTROL: Placebo

OUTCOME: Depression severity and depression remission

Secondary Outcome: Suicidality

METHODS (BRIEF DESCRIPTION):

- Patients were screened within 48 hours of presentation to Emergency Department.
- Patient criteria included MDD with acute suicidal ideation within the previous 24 hours.
  - Exclusion criteria included certain concurrent psychiatric disorders.
- Patients were randomized in a double-blinded fashion to one of two groups:
  - Esketamine intranasal spray via self-administered disposable nasal spray device in healthcare setting twice weekly for four weeks in addition to standard-of-care oral antidepressants.
    - Dose reduced for medication intolerance.
  - Placebo nasal spray via self-administered nasal device in healthcare setting twice weekly for four weeks in addition to standard-of-care oral antidepressants.
- Depression severity was measured with the Montgomery-Asberg Depression Rating Scale (MADRS) with scores ranging from 0 to 60, with higher scores indicating more severe depression.
  - Depression remission was defined as MADRS <12.
- Suicidality severity was measured with the Clinical Global Impression Scale for Severity of Suicidality (CGI-SS) with scores ranging from 0 to 6, with higher scores indicating more severe suicidality.
  - 0 indicates normal and 1 indicates questionable levels of suicidality.
- Efficacy raters were not involved in patient care and were separated from safety raters.

INTERVENTION (# IN THE GROUP): 89

COMPARISON (# IN THE GROUP): 94

FOLLOW UP PERIOD: 4-week treatment phase with 90 day follow up

RESULTS:

Primary Outcome –

- Esketamine decreased depression severity more than placebo (–16 vs –12, respectively; mean difference [MD] –3.9; 95% CI, –6.6 to –1.1).
- Esketamine decreased depression remission rates more than placebo on day 2 (MD 11%; 95% CI, 1.8–21).
  - The difference was not sustained by day 25 (MD 10%; 95% CI, –2.6 to 23).

Secondary Outcome –

- 86% of patients in the Esketamine group and 77% of patients in the placebo group had normal or questionable levels of suicidality by the end of the follow up period (no statistical analysis conducted).

LIMITATIONS:

- Dissociation is a side effect of Esketamine, which may have resulted in functional unblinding during the study.

- Previous trials have demonstrated significant placebo effect in anti-depression studies likely due to both frequency of provider interaction and patient expectations for treatment.
- Standard-of-care varied between regions (i.e., length of inpatient hospital stay or type of anti-depressants).

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The views expressed in this GEM are the authors' and do not reflect the official policy or position of the U.S. Army, the Tripler Army Medical Center, or the U.S. government.

Don't Be Tachy: Drink Your Coffee

Coffee Consumption and Incident Tachyarrhythmias Reported Behavior, Mendelian Randomization, and Their Interactions

Kim EJ, Hoffmann TJ, Nah G, Vittinghoff E, Delling F, Marcus G, et al. Coffee Consumption and Incident Tachyarrhythmias: Reported Behavior, Mendelian Randomization, and Their Interactions. *JAMA Intern Med*. 2021; 181(9):1185–1193.

KEY TAKEAWAY: Coffee consumption may decrease the incidence of arrhythmias, specifically atrial fibrillation and supra-ventricular tachycardia.

STUDY DESIGN: Prospective cohort study

LEVEL OF EVIDENCE: STEP 3

BRIEF BACKGROUND INFORMATION: It is commonly thought drinking coffee increases the risk of arrhythmias, but this hypothesis has not been explored in a research study before.

PATIENTS: Non-pregnant adults

INTERVENTION: Coffee drinking

CONTROL: No coffee drinking

OUTCOME: Development of tachyarrhythmias

METHODS (BRIEF DESCRIPTION):

- Participants were divided into eight groups based on self-reported daily cups of coffee consumed: 0, <1, 1, 2, 3, 4, 5, ≥6.
- Patients were 40–69 years old from UK National Health Services enrolled in the UK Biobank project.
- Participants were excluded if they had history of arrhythmias.
- Participants were followed for new onset of any of the following: Atrial fibrillation/flutter, supraventricular tachycardia, ventricular tachycardia, premature atrial complexes, and premature ventricular complexes.

INTERVENTION (# IN THE GROUP): 300,742

- <1 cup/day: 26,979
- 1 cup/day: 77,275
- 2 cups/day: 77,346
- 3 cups/day: 47,623
- 4 cups/day: 32,744
- 5 cups/day: 19,209
- ≥6 cups/day: 23,201

COMPARISON (# IN THE GROUP): 83,228

FOLLOW UP PERIOD: 8 years (mean 4.5 years)

RESULTS:

- For every additional cup of coffee consumed there was a 3% lower risk of any arrhythmia (HR 0.97; 95% CI, 0.96–0.98).
- The only individual arrhythmias associated with a statistically significant decrease for each additional cup of coffee consumption were:
  - Atrial fibrillation (HR 0.97; 95% CI, 0.96–0.98)
  - Supra-ventricular tachycardias (HR 0.96; 95% CI, 0.94–0.99)
- Additional analysis showed smokers had a significantly higher risk of arrhythmias (HR 1.1; 95% CI, 0.03–1.2).

LIMITATIONS:

- It is unknown if participants' daily coffee intake was consistent throughout the study.
- Caffeine content was not quantified in any type of coffee, with 19% of coffee drinkers reported using decaffeinated coffee and 56% reported using instant coffee. It is also possible that "non-coffee drinkers" were consuming other sources of caffeine.
- The mean follow-up may not have been long enough to assess for the development of later arrhythmias.

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A Shot in the Dark? Ultrasound-Guided vs Blind Steroid Injections

Comparing the Accuracy and Efficacy of Ultrasound-Guided versus Blind Injections of Steroid in the Glenohumeral Joint in Patients with Shoulder Adhesive Capsulitis

Raeissadat SA, Rayegani SM, Langroudi TF, Khoiniha M. Comparing the accuracy and efficacy of ultrasound-guided versus blind injections of steroid in the glenohumeral joint in patients with shoulder adhesive capsulitis. *Clin Rheumatol*. 2017; 36(4):933–940.

KEY TAKEAWAY: Compared with blind steroid injections ultrasound (US) guided steroid injections into the glenohumeral joint did not significantly improve accuracy, pain control, or function at one and four-weeks post injection. Additionally, accurately placed injections did not correlate with improved pain or function.

STUDY DESIGN: Single-blind randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Steroid injections are administered into joints for relief of symptoms. Injections have traditionally been done blindly. It is unknown if using US would provide greater accuracy and improve pain and function more than blind injections.

PATIENTS: Adults 33–77 (mean 59) years old, with adhesive capsulitis for ≥3 months

INTERVENTION: US guided steroid injections into glenohumeral joint

CONTROL: Blind steroid injections into the glenohumeral joint

OUTCOME: Accuracy, pain, and function

METHODS (BRIEF DESCRIPTION):

- Participants with adhesive capsulitis were randomized to two groups to receive glenohumeral joint steroid injection either blindly or using US.
  - Exclusions: History of shoulder surgery, inflammatory joint disease, history of previous fracture, hypersensitivity reaction to steroids, history of shoulder physical therapy, or an injection within the last three months.
- All injections were performed by the same physician with 15 years of experience via posterior-lateral approach.
- Injections consisted of 1 cc of 1% lidocaine, 1 cc of triamcinolone 40 mg/cc, and 3 cc of unionized contrast with 1 cc of distilled water.
- Immediately after injection shoulder x-rays were performed in both groups to assess accuracy of the injection.
- Injection placement was considered accurate if contrast material was seen in glenohumeral joint.
- The following information was gathered prior to injection and at one and four weeks after injection:
  - Pain severity via Visual Analog Scale (VAS; 1–10; 10=worse)
  - Functional status based on Oxford Shoulder Score (0–48; higher is better)
  - Five shoulder range of motions measured by goniometer (abduction, extension, flexion, internal, and external rotation)

INTERVENTION (# IN THE GROUP): 20

COMPARISON (# IN THE GROUP): 21

FOLLOW UP PERIOD: 4 weeks

RESULTS:

- There were no significant differences between the two groups in pain or function at one and four weeks except for extension.
  - The US group demonstrated significantly improved extension compared to the blind group at one week (mean change 11 degrees vs. 2.1 degrees; *P*=.01) and four weeks (mean change 12 degrees vs. 2.6 degrees; *P*=.01).
- US injections were not significantly more accurate than the blind group. (90% vs 76%; *P*=.24).
- Accurate injections did not improve pain or function compared to inaccurate injections.

LIMITATIONS:

- Injections were performed by a physician with 15 years of experience; therefore, these results may not be applicable to all physicians.
- Small sample size.
- All patients received Naproxen bid for 5 days after injections, which might have influenced VAS scores.

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