

GEMs of the Week



SPOTLIGHT

Ketamine Better Than Etomidate? No!

Silver Diamine Fluoride to the Rescue

The Power of Motion

Healing the Blues After Concussion

GABA Action Might Out a Patient in Femur Traction

Ketamine or Etomidate for Tracheal Intubation of Critically Ill Adults

Casey JD, Seitz KP, Driver BE, et al. Ketamine or Etomidate for Tracheal Intubation of Critically Ill Adults. *N Engl J Med*. Published online December 9, 2025. doi:10.1056/NEJMoa2511420

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KEY TAKEAWAY: Induction with ketamine in critically ill patients does not significantly reduce mortality compared to etomidate.

STUDY DESIGN: Multicenter, nonblinded randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Ketamine and etomidate are commonly used induction agents for intubation of critically ill patients. Some studies have suggested ketamine decreases mortality compared to etomidate, while other studies have shown no difference. This study was conducted to compare mortality between critically ill patients intubated with ketamine vs etomidate.

PATIENTS: Critically ill adults without trauma or known pregnancy

INTERVENTION: Ketamine up to 2.0 mg/kg

CONTROL: Etomidate up to 0.3 mg/kg

PRIMARY OUTCOME: 28-day in-hospital mortality
Secondary Outcome: Cardiovascular collapse from administration of induction agent until 2 minutes after intubation

METHODS (BRIEF DESCRIPTION):

- Patients were recruited from six emergency departments and eight intensive care units at six different medical centers in the United States.
- Adult patients (≥ 18 years old) who were critically ill and undergoing induction for tracheal intubation were included in the study.
- Patients who were pregnant, incarcerated, or required immediate intubation prior to randomization were excluded from this study along with trauma patients and patients for whom the treating clinician decided there was a specific indication/contraindication for ketamine or etomidate.

- Patients were randomized 1:1 to either ketamine or etomidate.
 - In the ketamine group, clinicians selected the dose with a median dose of 1.6 mg/kg.
 - In the etomidate group, clinicians selected the dose with a median dose of 0.28 mg/kg.
- The primary outcome was in-hospital death from any cause within 28 days of enrollment.
- The secondary outcome was cardiovascular collapse during the time interval from administration of induction agent until 2 minutes after intubation:
 - Systolic blood pressure (SBP) < 65 mmHg
 - New/increased vasopressor requirement
 - Cardiac arrest

INTERVENTION (# IN THE GROUP): 1,176

COMPARISON (# IN THE GROUP): 1,189

FOLLOW-UP PERIOD: Up to 28 days

RESULTS:

Primary Outcome –

- Ketamine did not significantly decrease 28-day mortality compared to etomidate (absolute risk difference [ARD] 0.8 percentage points; 95% CI, -4.5 to 2.9).

Secondary Outcome –

- Etomidate decreased cardiovascular collapse during intubation compared to ketamine (ARD 5.1; 95% CI, 1.9–8.3).

LIMITATIONS:

- This study was unblinded, which could influence assessment of outcomes or treatment decisions.
- This study excluded trauma patients, which limits external validity.
- 23% of patients in the ketamine group and 36% of patients in the etomidate group received doses at or above the highest recommended weight-based dosing; however, a dose-response relationship was not explored in the secondary outcomes, which may limit internal validity for lower doses.

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The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Army, Defense Health Agency, Department of Defense, or the U.S. Government.

Effect of Silver Diamine Fluoride on Caries Arrest and Prevention: The Caried Away School-Based Randomized Clinical Trial

Ruff RR, Barry-Godín T, Niederman R. Effect of Silver Diamine Fluoride on Caries Arrest and Prevention: The Caried Away School-Based Randomized Clinical Trial. *JAMA Netw Open.* 2023;6(2):e2255458. Published 2023 Feb 1. doi:10.1001/jamanetworkopen.2022.55458
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KEY TAKEAWAY: Silver diamine fluoride (SDF) is non-inferior to standard treatment for stopping progression of existing and preventing new dental caries.

STUDY DESIGN: Cluster- randomized, single-blind, noninferiority trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to single blind study design)

BRIEF BACKGROUND INFORMATION: CDC recommend dental sealants and topical fluoride as essential medications for treatment and prevention of dental caries. WHO additionally includes SDF as an essential medication for dental caries. This study investigates the effectiveness of a school-based SDF system for atraumatic restorative therapy for dental caries and prevention.

PATIENTS: School age children

INTERVENTION: SDF with standard fluoride varnish

CONTROL: Standard fluoride varnish with sealant and atraumatic restoration

PRIMARY OUTCOME: Dental caries arrest and prevention

METHODS (BRIEF DESCRIPTION):

- Children 5–13 years old from 47 New York City primary schools were recruited for a participant blinded cluster randomized (by school) trial.
- Schools included had a population with 50% Hispanic or Black ethnicity, 80% of students receiving reduced or lunch, and while all students received treatment, grades K-3 were included in the analysis.
- Patients not speaking English or enrolled in special education classes received care but were not included in the study.
- The mean age was 6.6 years old, 52% were girls, 64% identified as Hispanic or Black, and 29% had untreated decay at baseline.

- The treatment group received 5% fluoride varnish to all teeth and 38% SDF (2.2 mg/dose of fluoride) applied once to asymptomatic cavitary lesions and fissures and pits of all molars and bicuspids.
 - The comparison group received 5% fluoride varnish to all teeth, plus glass ionomer sealants to pits and fishers of bicuspid and molars and atraumatic restoration on asymptomatic caries.
- The primary outcome was the proportion of children with arrested caries and proportion of children with prevention which were defined by the following:
 - Failure of arrest occurred when a child had caries at baseline, received a treatment, and presented at follow up with untreated caries or a filling.
 - Prevention occurred if no caries were found in children without prior caries.
- Outcomes were determined at the person level; any new caries considered a failure (despite number of caries).
- The noninferiority margin was determined to be 10%.

INTERVENTION (# IN THE GROUP): 2,348

COMPARISON (# IN THE GROUP): 2,370

FOLLOW-UP PERIOD: Two years

RESULTS:

Primary Outcome –

- Patients who had SDF treatment had similar rates of arrest of caries compared to placebo care (mean proportion 0.56 vs 0.46, respectively; mean difference [MD] –0.11; 95% CI, –0.22 to 0.01; odds ratio [OR] 1.5; standard error [SE] 0.33; 95% CI, 0.91–2.4, meeting non-inferiority margin).
- Patients who had SDF treatment had similar risk of dental caries prevention (remaining caries free) compared to placebo (mean proportion 0.81 vs 0.82, respectively; MD 0.01; 95% CI, –0.04 to 0.06; OR 0.93; SE 0.14; 95% CI, 0.68–1.3, meeting noninferiority margin).

LIMITATIONS:

- There was a high number of participants loss to follow up, and imputed data was used (follow up rate was 46%).

- New cavities or cavity arrest was not differentiated between single or multiple teeth (binomial outcome).
- Randomization was based on entire school systems and may have differing socioeconomic status though background data was similar.
- At follow-up there were significantly more patients in the standard treatment group.
- The study did not include family history of dental caries which could be a risk factor for individual dental disease.

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The Power of Motion: Healing the Blues After Concussion

Adolescents with a High Burden of New-Onset Mood Symptoms after Sport-Related Concussion Benefit from Prescribed Aerobic Exercise, A Secondary Analysis of 2 Randomized Controlled Trials

Castellana MC, Burnett GJ, Gasper A, et al. Adolescents with a High Burden of New-Onset Mood Symptoms after Sport-Related Concussion Benefit from Prescribed Aerobic Exercise, a Secondary Analysis of 2 Randomized Controlled Trials. *Clin J Sport Med.* 2025;35(1):29-36. doi:10.1097/JSM.0000000000001242

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KEY TAKEAWAY: Early targeted aerobic exercise decreases post-concussive symptoms compared to stretching in a high mood symptom burden group. Aerobic exercise does not decrease post-concussive symptoms compared to stretching in a low mood symptom burden group.

STUDY DESIGN: Secondary analysis of two randomized controlled trials (RCTs)

LEVEL OF EVIDENCE: STEP 3 (downgraded due to secondary analysis of RCTs, non-validated classification tool for mood symptoms, and small number of patients in the high mood symptom groups)

BRIEF BACKGROUND INFORMATION: Sports-related concussions are common in adolescents and can lead to new mood symptoms, which can be the most difficult post-concussion symptoms to treat. This article presents a secondary analysis of two RCTs which evaluated the effect of aerobic exercise on the time to return to sport and the incidence of persisting post-concussive symptoms (PPCS), focusing on whether aerobic exercise also helps with post-concussive mood symptoms.

PATIENTS: Adolescents diagnosed with sports-related concussion

INTERVENTION: Aerobic exercise

CONTROL: Stretching program

PRIMARY OUTCOME: Incidence of post-concussive symptoms

Secondary Outcome: Length of symptom recovery time, symptom burden, post-concussive symptoms risk

METHODS (BRIEF DESCRIPTION):

- Adolescents 13–18 years old who presented within 10 days of a sport-related concussion were included in the study.

- They were excluded if they:
 - Scored low on the PCSS or if there was only a three-point difference between the current and preinjury symptoms.
 - Had a Glasgow coma scale <13, lesion on CT/MRI, focal neurologic sign consistent with lesion, or injury involving loss of consciousness for >30 minutes and/or post-traumatic amnesia for >24 hours.
 - Had an inability to exercise because of lower extremity orthopedic injury or increased cardiac risk.
 - Had a history of moderate to severe traumatic brain injury (TBI) or >3 prior mild TBIs.
 - Were prescribed medications to treat a preexisting mood or learning disorder.
- Participants were randomized 1:1 to a targeted heart rate (HR) aerobic exercise program or a placebo stretching program.
- Research assistants performed a symptom assessment using a questionnaire that included questions addressing mood.
- Participants had exercise tolerance assessed using the Buffalo Concussion Treadmill Test (BCTT).
- Participants performed a BCTT test every week and were prescribed a new target HR or progressive stretching prescription until they recovered or the intervention ended at 28 days.
- The primary outcome was measured by the presence of symptoms at day 28 using the PCSS or Post-Concussion Symptom Inventory. The symptoms measured included irritability, sadness, nervousness, and feeling more emotional. Each symptom was scored on a scale from 0–6, with a score of zero indicating resolution of mood symptoms.
- Length of symptom recovery time was measured in days it took until recovery and cleared to return to activity by weekly clinical evaluations by blinded physicians. The correlation between risk of developing PPCS in the high-burden group versus the low-burden group was also assessed.

INTERVENTION (# IN THE GROUP):

- High mood symptom burden: 22

- Low mood symptom burden: 80

COMPARISON (# IN THE GROUP):

- High Mood Symptom Burden: 20
- Low Mood Symptom Burden: 76

FOLLOW-UP PERIOD: 28 days

RESULTS:

Primary Outcome –

- Aerobic exercise decreased post-concussive symptoms in the high mood symptom burden group compared to stretching (hazard ratio [HR] 0.29; 95% CI, 0.12–0.68).
- Aerobic exercise did not decrease post-concussive symptoms in the low mood symptom burden group compared to stretching (HR 0.77; 95% CI, 0.55–1.1).

Secondary Outcome –

- There was no significant difference in the mean recovery time between the low mood symptom burden group and the high mood symptom burden group.
- Adolescents with high mood symptom burden had a significantly higher risk of developing post-concussive symptoms than those with low mood symptom burden (40% vs 13%, respectively; $P < .001$).

LIMITATIONS:

- The treating physicians were blinded to the treatment arm. However, due to the nature of the intervention, the research assistant who prescribed the exercise and the participants were not.
- The high and low symptom classifier is not validated.
- The questionnaire for mood symptoms was part of a screening questionnaire and not a diagnostic of clinical syndromes of depression or anxiety.
- The results should not be used to generalize to those who develop mood symptoms beyond the first 10 days after injury, those with preexisting mood disorders, adults or younger children, or the nonathletic population.
- It is a retrospective analysis from two previous trials not originally designed to measure mood symptom outcomes.
- There was exercise non-adherence in both trials.
- The second RCT was stopped early due to COVID.

- Pre-existing symptoms that were undiagnosed may have affected the studies.

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Gabapentinoids and Risk of Hip Fracture

Leung MTY, Turner JP, Marquina C, et al. Gabapentinoids and Risk of Hip Fracture. *JAMA Netw Open*.

2024;7(11):e2444488. Published 2024 Nov 4.

doi:10.1001/jamanetworkopen.2024.44488

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KEY TAKEAWAY: Gabapentinoid prescription use increases the risk of hip fracture in individuals ≥ 80 years old.

STUDY DESIGN: Case case-crossover analysis

LEVEL OF EVIDENCE: STEP 4

BRIEF BACKGROUND INFORMATION: Hip fractures in older adults increase disability and mortality.

Gabapentinoids have become an increasingly popular medication in the management of neuropathic pain specifically in elderly patients trying to avoid use of opioids due to the perception that they are a safer alternative. Known side effects of gabapentinoids are increased drowsiness, increased risk of falls, and with long term use, increased risk of osteopenia.

PATIENTS: Adults ≥ 50 years old hospitalized for first hip fracture

INTERVENTION: Gabapentinoid prescription prior to fracture

CONTROL: Patients hospitalized for hip fracture who did not receive a gabapentinoid prescription

PRIMARY OUTCOME: Risk of hip fracture

Secondary Outcome: Risk of hip fracture in patients with chronic kidney disease (CKD) and frailty

METHODS (BRIEF DESCRIPTION):

- The study included patients ≥ 50 years old, hospitalized for a hip fracture with no prior history of hip fracture before admission and received at least one dispensing of a gabapentinoid.
- Each case consisted of a patient that was compared to themselves during three different time periods, Day 1–60 (index period) and Day 121–180 (reference period) prior to fracture to assess for gabapentinoid use during that time.
- Days 61–120 were used as a washout period. This analysis was termed the “case case-crossover” analysis.
- To minimize bias, a crossover analysis was conducted where each patient case was

matched with five hip fracture control cases. This analysis was termed the “future-case-control case-crossover” analysis.

- The control cases were patients of similar age and sex.
- Exposure was defined as having at least one oral gabapentinoid prescription during the index and/or reference period. Dose, frequency and duration were not assessed.
- The control group consisted of patients who experienced a hip fracture at a later date that were a similar age and sex to each patient case (the “future-case-controls”). Gabapentinoid use was then assessed in the period leading up to the fracture.
- The primary outcome assessed hip fracture. This was verified as a hospital admission for new onset hip fracture during the time period of March 1, 2013, to June 30, 2018, in patients ≥ 50 years old.
- Subgroup analyses included frailty status, as determined by use of the Hospital Frailty Risk Score, > 80 years old or < 80 years old, and history of CKD based on hospital diagnosis codes.
- To account for other possible factors, concordant co-morbidities, sex and use of other medications affecting fall risk were noted.

INTERVENTION (# IN THE GROUP): 2,644

COMPARISON (# IN THE GROUP):

- Time control: 2,644
- Case control: 12,920

FOLLOW-UP PERIOD: 180 days

RESULTS:

Primary Outcome –

- Gabapentinoid use increased the risk of hip fracture compared to patients not taking gabapentinoids (odds ratio [OR] 2.0; 95% CI, 1.7–2.3).
- Gabapentinoid use increased the risk of hip fractures compared to patient not taking gabapentinoids after adjusting for confounders (adjusted odds ratio [aOR] 1.3; 95% CI, 1.1–1.6).

Secondary Outcome –

- Gabapentinoid use increased the risk of hip fracture in patients with CKD (OR 2.4; 95% CI, 1.7–3.5).

- Gabapentinoid use increased the risk of hip fracture in patients with increased frailty (OR 1.8; 95% CI, 1.3–2.3).
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LIMITATIONS:

- No confirmation of gabapentinoid compliance was obtained.
 - Long term effects of gabapentinoids on bone health were not evaluated.
 - Subgroup analysis of type of gabapentinoid is impossible since 94% of the patients in this study were taking pregabalin.
 - Given the study design, residual confounding cannot be eliminated.
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