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CuratED: The emergency medicine pharmacotherapy literature of 2024

Ryan Feldman [a,*], Brett Faine [b], Megan A. Rech [c], David E. Zimmerman [d], Tara Flack [e], Gavin T. Howington [f,g], Jessica Laub [h], Blake Porter [i], Giles W. Slocum [j], Anne Zepeski [b], Ruben D. Santiago [k], Jordan Woolum [f,g], James Krenz [k], Preeyaporn Sarangarm [l], Jennifer Koehl [m]

[a] Medical College of Wisconsin School of Pharmacy, Froedtert and the Medical College of Wisconsin, Department of Emergency Medicine Division of Medical Toxicology, Medical College of Wisconsin, USA
[b] Department of Emergency Medicine and Pharmacy Practice, University of Iowa, Iowa City, IA 52242, USA
[c] Department of Veterans Affairs, Center of Innovation for Complex Chronic Healthcare, Edward Hines, Jr. VA Hospital, Hines, IL 60141, USA
[d] Duquesne University School of Pharmacy, University of Pittsburgh Medical Center-Mercy Hospital, Room 311 Bayer Learning Center, 600 Forbes Avenue, Pittsburgh, PA 15282, USA
[e] Department of Pharmacy, IU Health Methodist Hospital, Indianapolis, IN 46202, USA
[f] Department of Pharmacy Practice and Science, University of Kentucky College of Pharmacy, Lexington, KY 40506, USA
[g] Department of Pharmacy Services, University of Kentucky HealthCare, Lexington, KY 40536, USA
[h] Department of Pharmacy, Ralph H. Johnson VA Medical Center, Charleston, SC 29412, USA
[i] Department of Pharmacy, University of Vermont Medical Center, Burlington, VT 05401, USA
[j] Department of Emergency Medicine and Department of Pharmacy, Rush University Medical Center, Chicago, IL 60612, USA
[k] Department of Pharmacy, Jackson Memorial Hospital, Miami, FL, USA
[l] Department of Pharmacy, University of New Mexico Hospital, Albuquerque, NM 87106, USA.
[m] Medical Science Liaison – Gastroenterology, Eli Lilly, Denver, CO, USA

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ABSTRACT

The purpose of this article is to summarize pharmacotherapy related emergency medicine (EM) literature indexed in 2024. Articles were selected utilizing a modified Delphi approach. The table of contents from predetermined journals were reviewed and independently evaluated via the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system by paired authors. Pharmacotherapy-related publications deemed to be GRADE 1A and 1B were reviewed by the collective group for inclusion in the review. This article synthesizes and evaluates findings from 11 randomized controlled trials, 10 guidelines, clinical policies, position statements, or consensus recommendations, and 7 meta-analyses, providing critical insight into their potential clinical impact. Covered topics include guideline updates on seizure prophylaxis in traumatic brain injury, corticosteroid use in sepsis and acute respiratory distress and antibiotic prophylaxis in trauma. Additional topics include updates on thrombolytic therapy for acute ischemic stroke, including tenecteplase versus alteplase, anticoagulation reversal strategies with andexanet alpha and prothrombin complex concentrate, and the use of tranexamic acid in traumatic brain injury, ketamine versus etomidate for intubation in critically ill adults, expert consensus on heart failure hospitalization management, geriatric emergency medication safety recommendations, and emerging data on dual antiplatelet therapy for stroke management.

1. Introduction

Remaining current with emergency medicine (EM) literature can be a challenge given the expansive scope of medical conditions that EM healthcare professionals encounter in their daily practice. In response, the Emergency Medicine PHARMacotherapy Research NETwork (EMPHARM-NET), a network of EM clinical pharmacist researchers across the country, began curating an annual review highlighting top EM pharmacotherapy articles [1-4]. This article is the 2024 update that summarizes the most pertinent pharmacotherapy-related EM literature indexed over the past year.

2. Methods

A modified Delphi approach was used to select included articles. Preselected journals (listed in Appendix A) relevant to EM were divided among pairs of authors. The table of contents from all 2024 publications were then reviewed independently by two reviewers to identify

* Corresponding author.
E-mail address: rfeldman@mcw.edu (R. Feldman).

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publications related to EM pharmacotherapy in adult patients. Each article was then evaluated by the two reviewers based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, a validated and objective tool used to appraise the quality of published articles into four levels: high, moderate, low, and very low [4]. Disagreements in assigned GRADE level between reviewers were reassessed, with the final determination made by the primary author (RF). Articles deemed to be GRADE 1A or 1B were considered for inclusion. Seventy-one publications met the inclusion criteria and were further reviewed for final inclusion by the full research team. Although the scope of EM is broad, literature focusing primarily on pharmacotherapy employed in the Emergency Department (ED) were given preference. In addition to GRADE scoring, clinical impact and the novelty of subject matter were taken into consideration by the research team. Selected articles were grouped into the following categories: resuscitation, trauma, traumatic brain injury (TBI) and intracranial hemorrhage (ICH), anticoagulation reversal, ischemic stroke, toxicology, and miscellaneous.

3. Resuscitation

3.1. ACC Expert Consensus Decision Pathway on Clinical Assessment, Management, and Trajectory of Patients Hospitalized With Heart Failure Focused Update: A Report of the American College of Cardiology Solution Set Oversight Committee [5]

Initial diuretic dosing is a critical consideration for emergency department practitioners managing acute heart failure. The 2024 ACC Expert Consensus highlights diuretic strategies, reinforcing common clinical practices. For patients already on outpatient loop diuretics, the recommended IV dose is 1 to 2.5 times the oral furosemide equivalent. The guidelines highlight data showing that initiating 2.5 times the home dose leads to greater fluid loss, more significant weight reduction, and improved dyspnea relief within 72 h. While the guidelines are not strictly prescriptive, they acknowledge that for diuretic-naïve patients, an initial IV furosemide dose of 40–80 mg daily is common. Diuretic dosing should continue to be individualized based on fluid status, kidney function, and age, while leveraging evidence-based strategies to optimize fluid removal and symptom relief in acute heart failure.

3.2. Ketamine Versus Etomidate as an Induction Agent for Tracheal Intubation in Critically Ill adults: a Bayesian meta-analysis [grade 1A] [6]

Ketamine and etomidate are commonly used induction agents for patients requiring rapid sequence intubation (RSI). Peri-intubation complications (e.g. hypotension, cardiovascular collapse, etc.) may occur and ketamine's effect on hemodynamics could reduce these complications. This meta-analysis was performed to estimate the probability that ketamine would reduce mortality in critically ill patients requiring RSI when compared with etomidate. In this robust analysis, there were significant differences in any clinical outcomes measured.

The authors included seven randomized trials and one propensity-matched study ($n = 2978$). The primary outcome was mortality at the longest follow-up available. The Bayesian random-effects meta-analysis showed that ketamine had an 83.2 % probability of reducing mortality compared to etomidate. However, it's relative risk (RR) of 0.93 for mortality, had a 95 % credible interval, (CrI) of 0.79–1.08, indicated the risk may be higher or lower and is not statistically significant. Sensitivity analyses and analysis of only randomized trials yielded similar results. This study provides updated evidence on the debate between ketamine and etomidate for critically ill patients undergoing RSI. The decision to use ketamine or etomidate should continue to be based on patient-specific factors and side effect profiles of each agent.

3.3. 2024 Focused Update: Guidelines on Use of Corticosteroids in Sepsis, Acute Respiratory Distress Syndrome, and Community-Acquired Pneumonia [7]

Systemic inflammation can lead to critical illness-related corticosteroid insufficiency (CIRCI), caused by dysregulation of the hypothalamus–pituitary–adrenal axis, altered cortisol metabolism, and glucocorticoid resistance in the tissues [8]. This syndrome is a commonly encountered occurrence in critically ill patients with acute respiratory distress syndrome (ARDS), community-acquired pneumonia (CAP), and sepsis. This guideline, written by a multispecialty task force of international experts in critical care medicine and endocrinology from the Society of Critical Care Medicine and European Society of Intensive Care Medicine, updates the previous 2017 guidelines by focusing on five clinical Population, Intervention, Control, and Outcomes (PICO) questions pertaining to whether corticosteroids should be administration in hospitalized patients with sepsis, ARDS or CAP [9]. It also examines optimal dosing and duration in sepsis and whether methylprednisolone is preferred in ARDS.

Systematic review and GRADE methodology were used to determine the answer to each question. Overall, the search resulted in the following number of randomized controlled trials in each disease state: 46 in sepsis, 18 in ARDS and 18 in CAP.

- Sepsis: Corticosteroids for adult patients with septic shock (conditional recommendation, low certainty evidence);
  - Avoid high-dose, short-duration regimens (>400 mg/d hydrocortisone equivalent for <3 days) (strong recommendation, low certainty).
- ARDS: Corticosteroids suggested for hospitalized adults (conditional recommendation, moderate certainty); no preference for methylprednisolone.
- CAP: Corticosteroids recommended for adults hospitalized with severe bacterial CAP (strong recommendation, moderate certainty).

These updated guidelines provide support for the use of corticosteroids in specific diseases states, while also guiding clinicians toward consideration for dosing, duration, and agent selection where evidence supports it.

4. Trauma

4.1. Prehospital Trauma Compendium: Fluid Resuscitation in Trauma - a Position Statement and Resource Document of NAEMSP [10]

The National Association of EMS Physicians (NAEMSP) recently provided position statements and resource documents on fluid resuscitation and vasopressors in trauma. NAEMSP recommends isotonic crystalloids as the preferred fluids for prehospital trauma, with the specific choice guided by operational factors (i.e. compatibility and availability). Permissive hypotension is considered reasonable in patients without TBI, while for those with TBI, correcting hypotension is a higher priority, targeting a systolic blood pressure (SBP) of at least 110 mmHg in adults, or above the 75th percentile of age-appropriate blood pressure in pediatrics, to maintain increased cerebral perfusion pressures. Large-volume (>2 L) crystalloid resuscitation should generally be avoided due to the risk of increased transfusion requirements, coagulopathy, and mortality. Warmed IV fluids may be considered as hypothermia in trauma patients is associated with worsening outcomes.

4.2. Prehospital Trauma Compendium: Vasopressors in Trauma - a Position Statement and Resource Document of NAEMSP [11]

Additionally, the NAEMSP included a position statement stating that vasopressors are not recommended for routine use in traumatic

hemorrhagic shock, due to the potential for harm. There is insufficient evidence to support or refute their use in neurogenic shock from spinal cord injury (SCI) or in TBI. However, current guidelines recommend maintaining a MAP of 85–90 mmHg in acute SCI using vasopressors if needed. Key components of trauma resuscitation include hemorrhage control, and the use of TXA to promote clot stabilization and reduce mortality. Resuscitation efforts should target mental status and perfusion, rather than arbitrary blood pressure values. Significant evidence gaps remain, particularly for prehospital vasopressor use and in pediatric trauma. These guidelines reinforce current standard of care practices, further research is needed to refine these recommendations and improve patient outcomes.

4.3. Antibiotic Prophylaxis in Trauma: Global Alliance for Infection in Surgery, Surgical Infection Society Europe, World Surgical Infection Society, American Association for the Surgery of Trauma, and World Society of Emergency Surgery Guidelines [12]

The use of antibiotic prophylaxis is crucial in many trauma scenarios; however, there is a recognized tendency toward overuse. To address this issue and minimize associated complications, several global organizations have developed comprehensive guidelines outlining the appropriate use of antibiotic prophylaxis in trauma care (Table 1).

These guidelines provide recommendations on the necessity and duration of antibiotic prophylaxis for different anatomical regions, including the head, thorax, abdomen, open fractures, burns, and skin wounds or bites. They continue to emphasize that in noninfected, clean wounds, and blunt trauma without surgery, antibiotics offer no proven benefit. While the guidelines do not specify particular antibiotic agents for most injuries, they align with existing American surgical guidelines in recommending prophylaxis for open fractures. These guidelines offer a concise and valuable review of antibiotic prophylaxis strategies based on injury type, aiding clinicians in making informed decisions about antibiotic use in trauma care.

4.4. Joint COT/OTA/ACEP/NAEMSP/NAEMT Position Statement Prehospital Antibiotic Administration for Suspected Open Fractures [13]

The American College of Surgeons Committee on Trauma recommends prophylactic antibiotic administration within one hour of hospital presentation to mitigate risks of fracture-related infections, including delayed bone healing and chronic infection. As data supports earlier administration with reduced complications, this joint position statement from several prehospital and emergency medicine medical organizations recommends that if it does not delay transport, the prehospital administration of a first-generation cephalosporin should be performed after management of life threats. They recommend this regardless of patient penicillin allergy status but recommend increased monitoring in those with a penicillin allergy. While the statement does not provide specific guidance for patients with a known cephalosporin allergy, the authors acknowledge that true cefazolin allergy is uncommon and generally mild. This position statement reinforces efforts to improve quality metrics related to early antibiotic administration in trauma through enhanced collaboration with EMS providers.

Table 1
Recommendations from the *Antibiotic Prophylaxis in Trauma Guidelines* [12].

Antibiotic Prophylaxis Recommendation	Traumatic Injury
Prophylaxis Not Recommended	• Nonoperative blunt trauma of the head, brain, thoracic, and abdominal injuries. • Blunt thoracic trauma needing chest tube placement.
Case-By-Case Consideration	• Burns: Routine prophylaxis is unnecessary; focus on irrigation and wound care. In severe burns, prophylaxis is recommended for patients undergoing mechanical ventilation or skin grafting. • Skin wounds and bites: Case-by-case basis; the priority is wound cleaning and tetanus/rabies prevention.
Prophylaxis Recommended	• Penetrating head, maxillofacial, thoracic, and abdominal trauma, especially when surgical exploration (e.g., thoracotomy, laparotomy) is required. • Penetrating trauma with chest tube • Patients with open fractures should receive antibiotics, with early administration being crucial.

5. TBI and ICH

5.1. Guidelines for Seizure Prophylaxis in Adults Hospitalized with Moderate–Severe Traumatic Brain Injury: A Clinical Practice Guideline [14]

The Neurocritical Care Society released guidelines on pharmacologic seizure prophylaxis for adult patients with moderate to severe TBI defined as an injury with acute radiographic abnormalities requiring hospitalization. Importantly this guideline is not applicable to patients with a history of clinical or electrographic seizures.

The guidelines suggest that prophylactic anti-seizure medication (ASM) may or may not be initiated during the index hospitalization, as evidence shows no significant benefit or harm regarding early seizures, late seizures, adverse events, or mortality (weak recommendation, low-quality evidence). This represents a shift from the 2017 Guidelines for the Management of Severe TBI, which explicitly recommended phenytoin for the prevention of early post-traumatic seizures within the first seven days [15].

If prophylactic ASM is used, the guidelines suggest levetiracetam over phenytoin or fosphenytoin (weak recommendation, very low-quality evidence), as levetiracetam may carry a lower risk of adverse events and fewer drug-drug interactions. The decision to initiate prophylactic ASM should be guided by patient-specific factors, including seizure risk, the potential severity of post-seizure complications (e.g., elevated intracranial pressure), and the adverse effects of ASM. If initiated, the guidelines recommend short courses (<7 days) rather than extended courses (>7 days) of ASM for seizure prophylaxis (weak recommendation, low-quality evidence). Clinicians may consider ASM optional in moderate to severe TBI based on this guidance. If ASM is used, short courses of levetiracetam (≤7 days) are preferred.

5.2. Efficacy and Safety of Tranexamic Acid in Traumatic Brain Injury: A Systematic Review and Meta-Analysis of Randomized Controlled Trials [grade 1A] [16]

A meta-analysis of 11 randomized controlled trials, including 11,299 patients, evaluated the efficacy and safety of TXA compared to placebo in patients with TBI. The primary outcomes assessed were mortality, clinical outcomes, and adverse events.

TXA did not significantly reduce mortality (risk ratio [RR] 0.92; 95 % CI 0.86–1.00; $p = 0.06$), nor did it improve clinical outcomes (RR 0.92; 95 % CI 0.78–1.09). Additionally, TXA was not associated with an increase in adverse events (RR 0.94; 95 % CI 0.82–1.07). However, TXA administration was linked to a significant reduction in hemorrhagic expansion (RR 0.83; 95 % CI 0.70–0.99) and hemorrhagic volume (standardized mean difference − 0.39; 95 % CI -0.60 to −0.18). Despite variations across studies in TXA dosing, timing of administration, and follow-up duration, heterogeneity in study endpoints remained minimal.

While this meta-analysis does not support a mortality benefit or overall improvement in clinical outcomes, it does indicate that TXA may be beneficial in reducing hematoma expansion and hemorrhagic volume without increasing adverse effects in TBI patients.

5.3. The Effects of Prehospital TXA on Mortality and Neurologic Outcomes in Patients with Traumatic Intracranial Hemorrhage: A Subgroup Analysis From the Prehospital TXA for TBI trial [grade 1B] [17]

This was a prespecified secondary analysis of the Prehospital TXA for TBI trial that was conducted to evaluate mortality outcomes and the effects of different TXA dosing strategies in patients with ICH. The original study included 966 patients selected by prehospital personnel based on Glasgow Coma Scale (GCS) assessments. This secondary analysis focused on 541 (56 %) patients with CT-confirmed ICH, who were randomized to receive one of three interventions: TXA 2 g IV bolus, TXA 1 g IV bolus followed by a 1 g IV infusion, or placebo, all within two hours of injury.

Patients receiving the 2 g IV bolus of TXA had a significantly lower mortality rate (17 %) compared to those receiving placebo (27 %), with an adjusted difference of −8.5 % (95 % CI -15.9 to −1.0). Similarly, mortality was reduced in the 2 g IV bolus group compared to the 1 g bolus +1 g infusion group (26 %), with an adjusted difference of −10.2 % (95 % CI -17.6 to −2.9). No significant differences were observed between groups in terms of adverse effects, six-month neurological outcomes, or ICH progression. However, the 2 g IV bolus group exhibited a significantly lower disability rating scale score at six months compared to the other two groups. These results suggest that, in patients with CT-confirmed ICH, TXA 2 g IV bolus administered within two hours of injury is preferable to other dosing regimens or placebo.

6. Anticoagulation reversal

6.1. Andexanet for Factor Xa Inhibitor–Associated Acute Intracerebral Hemorrhage (ANNEXA-I) [grade 1A] [18]

The American Heart Association/American Stroke Association guidelines currently recommend andexanet alfa (class 2a recommendation) for reversing the effects of direct oral anticoagulants (DOACs) in patients with ICH. The ANNEXA-I trial was a multi-centered, randomized controlled trial comparing andexanet alfa ($n = 224$) versus usual care ($n = 228$) (e.g., prothrombin complex concentrate (PCC]) in patients with DOAC-associated ICH. The primary outcome was hemostatic efficacy defined as a change in the hematoma volume of ≤20 % (excellent hemostatic efficacy) or ≤ 35 % (good hemostatic efficacy) within 12 h after baseline. The trial was halted at the pre-specified interim analysis, which showed significantly better hemostatic efficacy in the andexanet alfa group compared to usual care (67.0 % vs. 53.1 %; 95 % CI, 4.6 to 22.2; $p = 0.003$). There was no significant difference in the secondary outcome of 30-day mortality (27.8 % vs. 25.5 %, 95 % CI −5.05–10.0, $p = 0.51$). However, thrombotic events were significantly more frequent in the andexanet alfa group (10.3 % vs. 5.6 %, 95 % CI −0.1-9.2, $p = 0.048$). The trial had significant limitations, including numerous protocol changes such as modifications to eligibility criteria and outcomes, along with only 85.5 % of the usual care group receiving a PCCs. Additionally, the positive primary outcome was primarily driven by changes in hematoma volume, and no demonstrated improvement in patient-centered outcomes (e.g., death, functional outcome). While andexanet alfa demonstrated superior hemostatic efficacy, functional outcomes for patients were not impacted, and the benefit came with an increased risk of thrombotic events. As a result, the FDA is currently evaluating whether andexanet alfa should gain full approval.

6.2. Andexanet Alpha Versus Four-Factor Prothrombin Complex Concentrate in DOACs Anticoagulation Reversal: an Updated Systematic Review and Meta-Analysis [grade 1A] [19]

Following the findings from the ANNEXA-I trial, a revised systematic review and meta-analysis of twenty-two studies including randomized controlled trials (RCTs), propensity score matching (PSMs) analyses, and retrospective studies was conducted to assess the effectiveness of andexanet alfa or PCCs in reducing short-term all-cause mortality for DOAC reversal. Andexanet alfa did not improve short-term all-cause mortality compared to PCCs (RR: 0.71; 95 % CI 0.37–1.34). However, andexanet alfa was associated with higher rates of thromboembolic events in both RCTs (RR: 1.74; 95 % CI 1.09–2.77) and PSM studies (RR:1.71; 95 % CI 1.01–2.89). Significant limitations include heterogeneity among study outcomes and patient populations. In addition, due to infrequent reporting, the analysis was unable to assess disability as an outcome. The evidence suggests PCCs are a reasonable agent for DOAC reversal, as andexanet alfa does not improve short-term mortality and is associated with higher thromboembolic risk.

6.3. Safety and Efficacy of Fixed Versus Variable-dose Prothrombin Complex Concentrate for Emergent Reversal of Vitamin K Antagonists (VKAs): A Systematic Review and Meta-Analysis [grade 1B] [20]

4.4. Fixed- Versus *Variable-Dose Prothrombin Complex Concentrate for the Emergent Reversal of Vitamin K Antagonists: A Systematic Review and Meta-Analysis [grade 1B]* [20].

Two meta-analyses were published in 2024 evaluating the safety and efficacy of fixed-dosed (FD) PCCs for emergent reversal of VKAs. Both studies compared FD versus weight-based (WB) dosing strategies for VKA reversal. The first meta-analysis included 23 studies ($n = 2055$), of which 12 studies ($n = 1143$) compared FD versus WB. The primary outcomes of interest were attainment of goal INR, survival to discharge, and rate of thromboembolic events. FD achieved similar reversal for a goal INR <2.0 (Risk Difference (RD) -1 %; 95 % CI -7, 4), but were less likely to achieve reversal for a goal INR <1.6 (RD: −13 %; 95 % CI -21, −4). No significant differences were observed in survival to discharge or thromboembolic event rates.

The second meta-analysis included three RCTs ($n = 323$) and sixteen observational studies ($n = 1912$). Outcomes assessed were INR goal attainment, clinical hemostasis, in-hospital mortality, and thromboembolic events. Among observational studies, there was no difference between FD and WB to achieve a goal INR <2.0 (88.8 % vs. 92.4 %; OR, 0.7; 95 % CI, 0.4–1.2). However, FD was less effective than WB in achieving a goal INR <1.5 in both observational studies (64.6 % vs. 74.3 %; OR, 0.6; 95 % CI, 0.5–0.8;) and RCTs (66.7 % vs. 88.6 %; OR, 0.3; 95 % CI, 0.09–0.8). FD was associated with lower mortality compared to WB in both cohort studies (15.6 % vs. 18.8 %; OR, 0.8; 95 % CI, 0.6–1.03, high certainty) and RCT studies (4.7 % vs. 7.2 %; OR, 0.6; 95 % CI, 0.1–1.9, high certainty). Thromboembolic rates were lower in the FD observational studies (2.4 % vs. 4.4 %; OR, 0.5; 95 % CI, 0.3–1, high certainty) and among RCTs (1.2 % vs. 1.8 %; OR, 0.7; 95 % CI, 0.1–3.8, moderate certainty).

Both analyses concluded that FD was effective in achieving an INR goal of <2.0 but were less likely to achieve stricter INR targets of <1.5 or < 1.6. However, given that FD was associated with lower mortality and fewer thromboembolic events, FD remains an appealing alternative to WB dosing strategies with the added benefit of lowering cost associated with PCC utilization.

7. Ischemic stroke

Tenecteplase Versus Alteplase

Comparison of intravenous thrombolysis (IVT) with alteplase and tenecteplase (TNK) in patients with acute ischemic stroke (AIS) within 4.5 h of last known well remains an area of ongoing research. Over the past year, three clinical trials have examined whether TNK 0.25 mg/kg (maximum dose 25 mg) is non-inferior, or potentially superior, to alteplase 0.9 mg/kg (maximum dose 90 mg) in AIS management.

7.1. Tenecteplase Versus Alteplase for Thrombolysis in Patients Selected by Use of Perfusion Imaging Within 4·5 h of Onset of Ischaemic Stroke (TASTE): a Multicentre Randomized, Controlled, Phase 3 Non-inferiority Trial [grade 1B] [21]

The TASTE trial ($n = 601$) was an open-label, phase 3, multicenter, randomized, non-inferiority trial conducted at 35 international stroke centers. Eligible patients presented within 4.5 h of last known well with a mismatch ratio greater than 1.8 on CT perfusion. Participants were randomized to receive IV TNK or alteplase. The primary outcome was the proportion of patients achieving a modified Rankin Scale (mRS) score of 0–1 at 90 days.

The trial was terminated early following publication of other studies demonstrating TNK's non-inferiority to alteplase. In the per-protocol analysis, 59 % of TNK recipients achieved mRS 0–1 at 90 days, compared to 56 % in the alteplase group (SRD 0.05 [−0.02 to 0.12], test for non-inferiority $p = 0.01$), confirming non-inferiority. However, the superiority of TNK was not demonstrated. Mortality at 90 days (7 % TNK vs. 4 % alteplase) and symptomatic ICH rates (3 % TNK vs. 2 % alteplase) were not significantly different between groups.

7.2. Tenecteplase vs Alteplase for Patients With Acute Ischemic Stroke The ORIGINAL Randomized Clinical Trial [grade 1A] [22]

The ORIGINAL trial ($n = 1465$) was a multicenter, randomized, open-label, phase 3 non-inferiority study conducted across 55 sites in China. Patients with an initial National Institutes of Health Stroke Scale (NIHSS) score of 1–25 presenting within 4.5 h of last known well were included. Participants were randomized to TNK or alteplase.

TNK was found to be non-inferior to alteplase for mRS 0–1 at 90 days (adjusted RR, 1.03 [95 % CI, 0.97–1.07]; $p = 0.003$). No statistically significant differences were observed in functional outcomes at 24 h or 90 days. Symptomatic ICH occurred in 1.2 % of patients in both groups (RR, 1.01 [95 % CI, 0.37–2.7]). Mortality at 90 days was comparable (4.6 % TNK vs. 5.8 % alteplase).

7.3. Tenecteplase Versus Alteplase for Acute Stroke Within 4.5 h of Onset (ATTEST-2): a Randomized, Parallel-Group, Open-label Trial [grade 1B] [23]

The ATTEST-2 trial ($n = 1777$) was a prospective, randomized, open-label trial conducted at 39 stroke centers in the UK. Patients with suspected AIS and prior functional independence (mRS 0–2) were randomized to TNK or alteplase. The primary outcome was mRS score distribution at 90 days.

TNK was non-inferior to alteplase for mRS score distribution (OR, 1.07 [95 % CI, 0.9–1.27]). Absolute increase in excellent mRS scores (0–1) was 2.03 % for TNK (adj. OR, 1.05 [95 % CI, 0.85–1.3)], but superiority was not achieved. Mortality (8 % TNK vs. 8 % alteplase) and ICH rates (11 % TNK vs. 9 % alteplase) were similar.

7.4. Tenecteplase vs Alteplase in Acute Ischemic Stroke Within 4.5 Hours: A Systematic Review and Meta-Analysis [grade 1A] [24]

Collectively, recent trials repeatedly demonstrate non-inferiority of TNK compared to alteplase in AIS within 4.5 h from last known well. To distill all previously published data and provide more robust legitimacy for the use of TNK in AIS, a systematic review and meta-analysis was conducted that evaluated all available randomized controlled trials investigating the efficacy and safety of TNK 0.25 mg/kg compared to standard alteplase dosing for AIS. This trial did include studies that allowed a dose greater than 25 mg for the maximum TNK dose.

The systematic review/meta-analysis synthesized data from 11 randomized controlled trials ($n = 3788$ TNK; $n = 3757$ alteplase). The mean NIHSS score was 11 in both cohorts, with an average age of 69 years in the TNK group and 70 years in the alteplase group. Mean time from last known well to treatment was 158 min.

TNK recipients were more likely to achieve mRS 0–1 at 90 days compared to alteplase (RR, 1.05 [95 % CI, 1.01–1.1]; $p = 0.012$). TNK was associated with improved odds of reduced disability at 90 days (cOR, 1.1 [95 % CI, 1.01–1.19]; $p = 0.034$), with no significant differences in symptomatic ICH or all-cause mortality.

7.5. Summary

TNK at 0.25 mg/kg (max 25 mg) has consistently demonstrated non-inferiority to alteplase for AIS within 4.5 h of symptom onset, with recent meta-analysis data suggesting potential superiority for functional outcomes. Current guidelines from the American Heart Association/American Stroke Association endorse TNK as an alternative to alteplase for eligible patients, while the European Stroke Organization and UK National Clinical Guidelines for Stroke provide stronger recommendations for TNK [25-27].

IV Thrombolytics (IVT) with Thrombectomy

Intravenous thrombolysis for patients undergoing thrombectomy remains an area of ongoing debate. The American College of Emergency Physicians (ACEP) published a clinical policy in 2024 recommending that IVT should be considered before thrombectomy in eligible patients (Level B recommendation) [28]. Recently, one major study and one meta-analysis evaluated the combination of IVT with thrombectomy versus thrombectomy alone in AIS.

7.6. Time to Treatment With Intravenous Thrombolysis Before Thrombectomy and Functional Outcomes in Acute Ischemic Stroke. A Meta-Analysis [grade 1B] [29]

A meta-analysis of six randomized clinical trials conducted across 190 sites in 15 countries assessed the efficacy of IVT plus thrombectomy compared to thrombectomy alone, with a particular focus on how the timing of treatment from symptom onset influenced outcomes. The study included 2313 patients, of whom 1160 received IVT plus thrombectomy and 1153 underwent thrombectomy alone. Among those in the IVT group, most ($n = 1032$) received alteplase 0.9 mg/kg (maximum dose 90 mg). The median time from symptom onset to expected IVT administration was 2 h and 28 min (IQR, 1 h 46 min to 3 h 17 min).

The primary outcome was disability at 90 days, measured using the mRS. A significant interaction was observed between time from symptom onset to IVT administration and the treatment effect. For every 1-h delay in IVT administration, the likelihood of better functional outcomes decreased (ratio of adjusted common OR 0.84; 95 % CI, 0.72–0.97). The greatest benefit was observed with early IVT administration at 1-h post-onset (adjusted common OR 1.49; 95 % CI, 1.13–1.96). These findings suggest that the benefit of IVT in conjunction with thrombectomy is time-dependent, with the greatest functional improvement at 90 days seen when IVT is administered as early as possible after symptom onset.

7.7. Tenecteplase for Stroke at 4.5 to 24 Hours with Perfusion-Imaging Selection (TIMELESS) [grade 1A] [30]

The TIMELESS trial ($n = 458$) was a multicenter, double-blind, randomized, placebo-controlled trial conducted at 112 centers in the United States and Canada. The study enrolled AIS patients (NIHSS score ≥ 5) with evidence of middle cerebral artery (MCA) or internal carotid artery (ICA) occlusion and salvageable brain tissue, as assessed by CT perfusion imaging or perfusion-diffusion MRI. Eligible participants were 18 years or older, had a pre-stroke mRS score of 0 to 2, and could receive TNK 0.25 mg/kg (maximum dose 25 mg) or placebo between 4.5 and 24 h after last known well.

The median NIHSS score at baseline was 12 (IQR, 8–17) in the TNK group and 12 (IQR, 8–18) in the placebo group. The median time from last known well to randomization was 12.3 h (IQR, 9.2–15.6) in the TNK group and 12.7 h (IQR, 8.7–16.5) in the placebo group.

Endovascular thrombectomy was performed in 77.2 % of TNK-treated patients and 77.4 % of placebo-treated patients.

There was no difference in the primary outcome of median mRS score at 90 days between groups (median mRS 3 in each group, adjusted common OR 1.13; 95 % CI, 0.82–1.57). The incidence of symptomatic ICH within 36 h was also similar between groups (3.2 % TNK vs. 2.3 % placebo), as were 90-day mortality rates (19.7 % TNK vs. 18.2 % placebo). These results suggest that administration of TNK in AIS patients with MCA or ICA occlusions 4.5 to 24 h after symptom onset provided no clinical benefit, particularly given that the majority of participants also underwent thrombectomy. This study reinforces the lack of utility in growing evidence questioning the utility of IVT beyond 4.5 h in AIS patients undergoing thrombectomy.

7.8. Summary

The role of IVT in AIS patients undergoing thrombectomy remains debated. A meta-analysis indicates that early IVT administration significantly improves functional outcomes when given within the first few hours after symptom onset. However, the TIMELESS trial suggests that IVT with TNK beyond 4.5 h offers no additional benefit in patients undergoing thrombectomy. These findings highlight the importance of patient selection and time-sensitive intervention when considering IVT in the thrombectomy population.

IV Thrombolytics in Minor Stroke

While IVT is a cornerstone of AIS treatment, its primary benefit is improving functional outcomes. This has led to debate about its role in minor AIS, where patients often have good baseline function and may not experience significant disability. Recent trials have questioned whether thrombolytics provide meaningful benefits in this population, particularly in those with low NIHSS scores.

7.9. Tenecteplase Versus Standard of Care for Minor Ischaemic Stroke with Proven Occlusion (TEMPO-2): a Randomized, Open Label, Phase 3 Superiority Trial [grade 1A] [31]

The TEMPO-2 trial ($n = 886$) was a multicenter, prospective, parallel-group, open-label, randomized controlled trial with blinded outcome assessment conducted across 48 international hospitals. The study evaluated TNK 0.25 mg/kg (maximum dose 50 mg) compared to guideline-based non-thrombolytic standard care in patients with minor AIS (NIHSS 0–5) presenting within 12 h of symptom onset. Eligible participants had a baseline mRS of 0–2 and evidence of an intracranial occlusion or a focal perfusion abnormality relevant to their presenting symptoms. Patients who met standard IVT criteria or had contraindications to IVT were excluded.

The primary outcome was the return to baseline neurological function, defined as an mRS score of 0–1 for those with a pre-morbid mRS of 1 or 0–2 for those with a pre-morbid mRS of 2 at 90 days. The median baseline NIHSS score was 2 (IQR, 1–3) in both the TNK group ($n = 432$) and control group ($n = 452$). Time from symptom onset to treatment was similar between groups (TNK: median 293 min, IQR 165–453; control: median 311 min, IQR 184–495). Thirty-four patients in the TNK group received doses exceeding 25 mg. The majority of control group patients received dual antiplatelet therapy (DAPT) with aspirin and clopidogrel ($n = 259$), while others received aspirin monotherapy ($n = 106$).

The trial was stopped early due to futility. In the intention-to-treat analysis, no significant difference was observed in the proportion of responders between TNK and control groups after adjusting for age, sex, baseline NIHSS, and time to randomization (adjusted RR 0.96; 95 % CI, 0.89–1.04). However, TNK treatment was associated with higher rates of symptomatic ICH compared to the control group (2 % vs. <1 %; RR 4.2; 95 % CI, 0.9–19.6) and increased mortality (5 % TNK vs. 1 % control; adjusted HR 3.8; 95 % CI, 1.4–10.2). These findings suggest that TNK treatment in patients with minor AIS and intracranial occlusion within 12 h of symptom onset provided no benefit and was potentially harmful. Notably, a subset of patients received TNK 0.25 mg/kg at doses exceeding the recommended maximum of 25 mg, which may have influenced outcomes.

7.10. Dual Antiplatelet Versus Alteplase for Early Neurologic Deterioration in Minor Stroke With Versus Without Large Vessel Occlusion: Prespecified Post Hoc Analysis of the ARAMIS Trial [grade 1A] [32]

The ARAMIS trial was a multicenter, noninferiority study comparing DAPT with IV alteplase in patients with minor, non-disabling acute ischemic stroke (AIS). The trial established the noninferiority of DAPT for functional outcomes at 90 days, prompting a post-hoc analysis to evaluate treatment effects based on the presence or absence of large vessel occlusion (LVO). Patients were divided into LVO and non-LVO groups and stratified by treatment (DAPT or alteplase). Those without computed tomography angiography (CTA) or magnetic resonance angiography (MRA) at admission to confirm the responsible artery and degree of stenosis were excluded.

The analysis included 480 patients: 36 in the LVO group (13 treated with DAPT, 23 with alteplase) and 444 in the non-LVO group (197 treated with DAPT, 247 with alteplase). In the non-LVO group, DAPT was associated with significantly lower rates of early neurological deterioration compared to alteplase (0.5 % vs. 5.7 %; adjusted risk difference − 4.8 %, 95 % CI, −6.9 % to −2.6 %). No significant difference was observed in the LVO group (15.4 % vs. 13.0 %; adjusted risk difference 2.3 %, 95 % CI, −17.6 % to 22.3 %). Additionally, there was no significant difference in functional outcomes (mRS scores) at 90-day, based on receipt of DAPT or alteplase, in either the LVO or non-LVO groups. In the non-LVO group, DAPT was associated with a lower risk of bleeding events than alteplase (0.5 % vs. 7.7 %; adjusted risk difference − 6.4 %, 95 % CI, −8.9 % to −3.9 %).

These findings suggest that for patients with minor, non-disabling AIS, DAPT may be safer and as effective as alteplase, particularly in the absence of LVO. However, given the exploratory nature of this post-hoc analysis, results should be interpreted cautiously.

8. Toxicology

8.1. Effectiveness of Intramuscular Naloxone 1600 μg in Addition to Titrated Intravenous Naloxone 100 μg for Opioid Poisoning: a Randomized Controlled Trial [grade 1A] [33]

Naloxone is the primary antidote for opioid toxicity. Recently, there has been a push for longer-acting opioid reversal agents such as nalmefene; however, much of the supporting data comes is sponsored by drug manufacturers with a vested interest in promoting the idea that traditional reversal agents are insufficient for sustained reversal [34,35]. Concerns regarding prolonged opioid withdrawal with long acting agents have also been raised by major toxicology organizations [36]. Given these concerns, researchers have sought to optimize naloxone dosing strategies to balance effective opioid reversal with minimizing withdrawal and the need for continuous infusions.

This single-center, double-blind, randomized, placebo-controlled trial evaluated the effectiveness of intramuscular (IM) naloxone 1600 μg in addition to titrated intravenous (IV) naloxone in patients over 17 years of age with respiratory depression due to suspected opioid poisoning in the emergency department (ED). A total of 136 patients were randomized (placebo, $n = 67$; IM naloxone, $n = 69$). Patients who received IM naloxone experienced significantly less respiratory depression within four hours compared to those receiving placebo (41 % vs. 72 %; 95 % CI: 13 % to 46 %; $p < 0.001$). Additionally, IM naloxone recipients were less likely to require a continuous naloxone infusion (7 % vs. 37 %; $p < 0.001$).

Study limitations included its single-center design and the predominant opioid exposure being diacetylmorphine (heroin), with no cases

of fentanyl exposure. The authors concluded that the addition of 1600 μg of IM naloxone to titrated IV naloxone reduced respiratory depression recurrence at four hours and decreased the need for naloxone infusions. However, its applicability to fentanyl overdose remains unclear.

9. Miscellaneous

9.1. Peripheral Nerve Blocks in the Preoperative Management of Hip Fractures: A Systematic Review and Network Meta-Analysis [grade 1A] [37]

Severe pain from hip fractures is associated with increased morbidity and healthcare costs. Multiple peripheral nerve block types exist, and it is unclear which block performs best. This network meta-analysis of 63 randomized studies ($n = 4778$) evaluated nerve block effectiveness for preoperative pain was conducted to evaluate the comparative efficacy of peripheral nerve block types for preoperative pain of hip fractures. Patients >16 years receiving any local anesthetic were included, excluding combination blocks.

Pain scores two hours post-block (50 studies, $n = 3540$) were lower with femoral nerve, 3-in-1, fascia iliaca, and pericapsular nerve group blocks vs. no block (SMDs: −1.1 to −2.3). No difference in morphine use was found between block types and no block. Hospital stay, satisfaction, and adverse events varied. High bias risk and diverse treatment strategies use in studies limit strong conclusions. Nerve blocks remain an important tool in a multimodal pain management strategy.

9.2. Geriatric Emergency Medication Safety Recommendations (GEMS-Rx): Modified Delphi Development of a High-Risk Prescription List for Older Emergency Department Patients [38]

Half of patients aged 65 and older discharged from the emergency department (ED) are prescribed new medications, some of which carry a high risk of causing adverse drug events in this vulnerable population. To identify medication classes that should be avoided in older ED patients, a group of 10 ED physicians and one pharmacist reviewed the 2019 American Geriatrics Society Beers Criteria. Using a modified, three-round Delphi consensus process, the group developed a list of high-risk medications. In the first round, medications were graded based on priority for avoidance. The second round assessed the risk of short-term adverse events and the potential to avoid these risks. In the third round, the panel identified reasonable medical indications for high-risk medication use. The final list of high-risk medications to avoid prescribing to geriatric patients at ED discharge includes barbiturates, benzodiazepines, first-generation antihistamines, metoclopramide, first-generation antipsychotics, benzodiazepine receptor agonist hypnotics (*Z*-drugs), skeletal muscle relaxants, and sulfonylureas. The expert panel also outlined clinical scenarios where these medications might be appropriate and recommended safer alternatives for older adults. When discharging older adults from the ED, avoid high-risk medications unless necessary and refer to this document for safer alternatives.

9.3. Clinical Policy: Critical Issues in the Evaluation and Management of Adult Out-of-Hospital or Emergency Department Patients Presenting with Severe Agitation [39]

An American College of Emergency Physicians (ACEP) subcommittee conducted a systematic review to identify the optimal parenteral (IV or IM) medication or combination of medications for the acute management of severe agitation in adult out-of-hospital or ED patients. Due to methodological inadequacies, no out-of-hospital studies were included in the review. For severely agitated ED patients, the subcommittee concluded that a combination of droperidol and midazolam offers the most favorable balance of rapid sedation and side effect profile (level B). If a single agent is required, droperidol is preferred (level B). When droperidol is unavailable, an atypical antipsychotic is the next best option (level B). In situations where safety necessitates the use of ketamine, it should be administered in a controlled setting where immediate hemodynamic monitoring and advanced airway management are available (level C, consensus recommendation). No recommendations for or against the use of specific agents in the out-of-hospital setting or specific recommendations for patients above the age of 65 years could be made. ACEP also emphasized the need for further research to explore the safety and efficacy of various dosing regimens, medication combinations, and their use in vulnerable populations. For severe agitation, assessment should be based on available resources and patient factors; droperidol, midazolam, and ketamine remain valuable tools, but require appropriate monitoring.

10. Conclusion

This article summarizes key findings from 28 publications, including 11 randomized controlled trials, 10 guidelines, clinical policies, position statements, or consensus recommendations, and 7 meta-analyses. It provides clinicians with updated evidence and recommendations for medical treatments in the emergency department, ensuring they remain informed on the latest advancements in emergency medicine pharmacotherapy.

CRediT authorship contribution statement

Ryan Feldman: Writing – review & editing, Writing – original draft, Project administration, Investigation, Formal analysis, Data curation. **Brett Faine:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Megan A. Rech:** Writing – review & editing, Writing – original draft, Data curation. **David E. Zimmerman:** Writing – review & editing, Writing – original draft, Data curation. **Tara Flack:** Writing – review & editing, Writing – original draft, Data curation. **Gavin T. Howington:** Writing – review & editing, Writing – original draft, Data curation. **Jessica Laub:** Writing – review & editing, Writing – original draft, Data curation. **Blake Porter:** Writing – review & editing, Writing – original draft, Data curation. **Giles W. Slocum:** Writing – review & editing, Writing – original draft, Data curation. **Anne Zepeski:** Writing – review & editing, Writing – original draft, Data curation. **Ruben D. Santiago:** Writing – review & editing, Writing – original draft, Data curation. **Jordan Woolum:** Writing – review & editing, Data curation. **James Krenz:** Writing – review & editing, Data curation. **Preeyaporn Sarangarm:** Writing – review & editing, Data curation. **Jennifer Koehl:** Writing – review & editing, Data curation.

Declaration of competing interest

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Appendix A. Supplementary data

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