Important Articles in Internal Medicine

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Disclosure of Financial Relationships

- No relationships to disclose

7 Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

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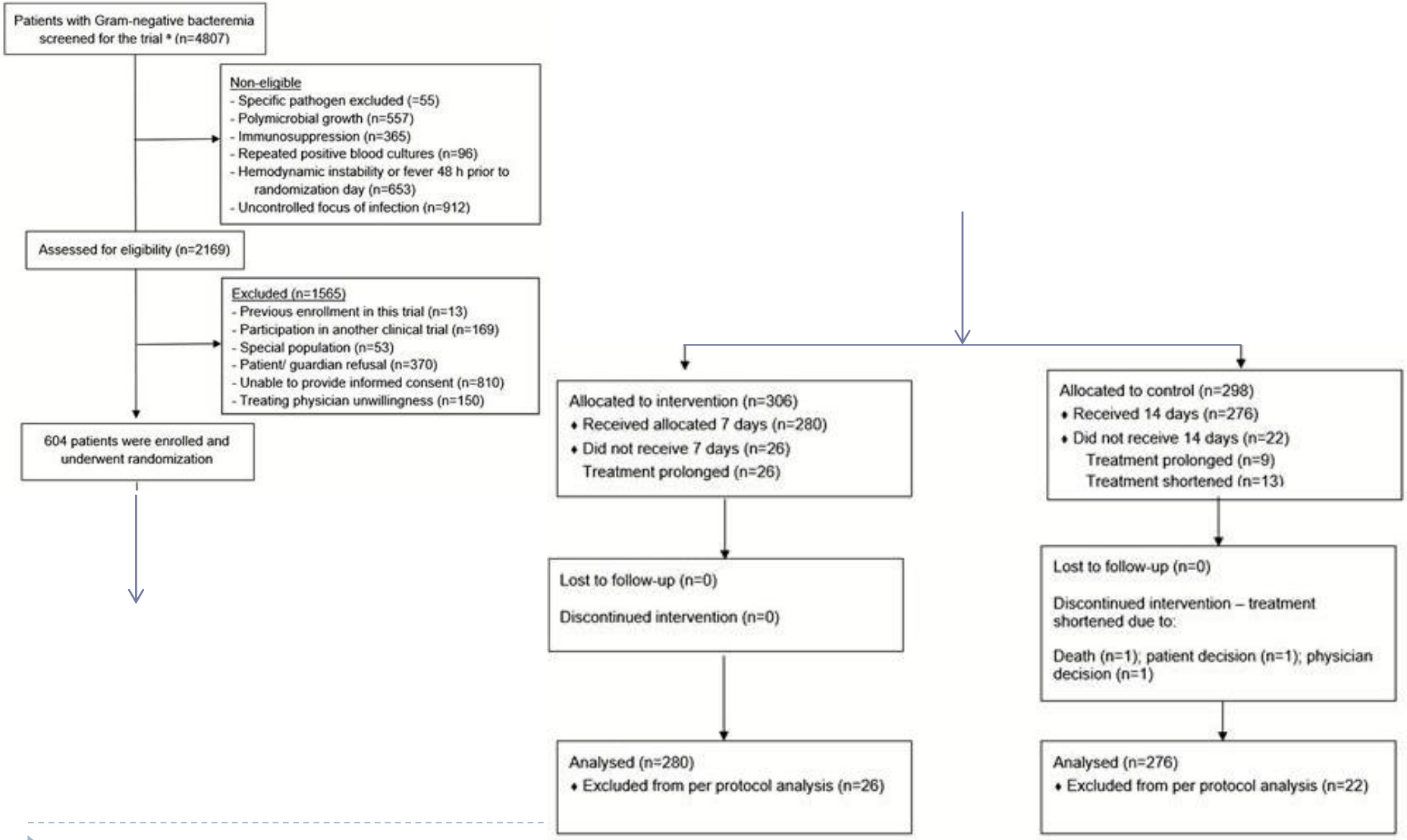
7 vs 14 Days of Antibiotics for GNR bacteremia

- Randomized, multicenter, open-label non-inferiority trial for inpatients with gram-negative bacteremia
- Included people with UTI, intra-abdominal, respiratory tract, central venous catheter, or skin/soft tissue infection, or unknown source of bacteremia
- Excluded patient with uncontrolled focus of infection, polymicrobial infections, immunosuppression, or specific pathogens (Brucella, Salmonella)
- Patients were randomized at day 7 of covering antibiotic therapy to receive either 7 or 14 days of treatment

7 vs 14 Days of Antibiotics for GNR bacteremia

- Outcomes measured
  - Mortality
  - Clinical failure
  - Relapse
  - Local suppurative complications or distant complications
  - Readmission
  - Extended hospital stay (>14 days)

7 vs 14 Days of Antibiotics for GNR bacteremia



7 vs 14 Days of Antibiotics for GNR bacteremia

Table 2. Outcomes of 7 Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-Negative Bacteremia

Outcome	Short Arm (7 d) (n = 306)	Long Arm (14 d) (n = 298)	Risk Difference (95% CI)	*P* Value
Primary outcome	140 (45.8)	144 (48.3)	−2.6 (−10.5 to 5.3)	.527
90-d all-cause mortality	36 (11.8)	32 (10.7)	1.0 (−4.0 to 6.1)	.702
Readmissions	119 (38.9)	127 (42.6)	−3.7 (−11.5 to 4.1)	.363
Extended hospitalization beyond 14 d	15 (4.9)	19 (6.4)	−1.5 (−5.1 to 2.2)	.483
Distant complications	2 (0.7)	1 (0.3)	…	1.0
Relapse of bacteremia	8 (2.6)	8 (2.7)	−0.07 (−2.6 to 2.5)	.957
Suppurative complications	16 (5.2)	10 (3.4)	1.8 (−1.4 to 5.1)	.257
14-d mortality	7 (2.3)	4 (1.3)	0.95 (−1.42 to 3.44)	.288
28-d mortality	15 (4.9)	13 (4.4)	0.54 (−2.98 to 4.06)	.753
New clinically or microbiologically documented infection	70 (22.9)	68 (22.8)	0.06 (−6.6 to 6.8)	.987
Functional capacity: needs assistance/dependent in ADL or bedridden at 30 d	150 (51.4) (n = 292)	163 (57.2) (n = 285)	−5.8 (−13.9 to 2.3)	.031
Resistance development	33 (10.8)	29 (9.7)	1.0 (−3.7 to 5.9)	.690
Time to return to baseline activity, wk (90 d)	2 (0–8.3) (n = 218)	3 (1–12) (n = 222)	…	**.010**
Total hospital days (90 d from randomization)—survivors	3 (1–9) (n = 270 alive at day 90)	3.5 (1–10) (n = 266 alive at day 90)	…	.923
Total hospital days (90 d from randomization)—all	4 (1–10)	4 (1–12)	…	.603
Duration of appropriate antibiotic therapy for bacteremia	7 (7.0–8.0)	14.0 (14.0–14.0)	…	**< .001**
Total antibiotic days from culture collection to day 90 postrandomization	10.0 (9.0–18.0) (n = 270 alive at day 90)	16.0 (15.0–22.0) (n = 266 alive at day 90)	…	**< .001**
Adverse events				
Acute kidney injury	14 (4.6)	12 (4.0)	0.5 (−2.7 to 3.8)	.842
Liver function abnormalities	16 (5.2)	20 (6.7)	−1.5 (−5.3 to 2.3)	.494
Diarrhea during hospital stay	17 (5.6)	23 (7.7)	−2.2 (−6.1 to 1.8)	.285
Diarrhea until day 90[a]	49 (16)	54 (18.1)	−2.1 (−8.1 to 3.9)	.491
Rash	2 (0.7)	4 (1.4)	…	.445
Clostridium difficile infection	3 (1.0)	1 (0.3)	…	.322

Data are presented as no. (%) unless otherwise indicated. Values in bold indicate statistically significant difference.

Abbreviations: ADL, activities of daily living; CI, confidence interval.

[a]Diarrhea is defined as >3 episodes per day for at least 2 days.

7 vs 14 Days of Antibiotics for GNR bacteremia

- Study showed 7 days of antibiotic therapy to be non-inferior to 14 days in terms of mortality, clinical failure, readmissions, and prolonged hospitalization
- Rates of superinfections, development of resistance, and adverse events were not significantly different between the two groups
- A more rapid return to baseline activity was documented for the short-duration antibiotic arm (2 vs 3 days).

7 vs 14 Days of Antibiotics for GNR bacteremia

- Limitations
  - Included mostly Enterobacteriaceae as offending pathogens (~90%) which limits applicability for other bacteria including Pseudomonas and Acinetobacter
  - Could not show the impact of reducing antibiotic use on resistance
- Conclusion
  - 7 days was non-inferior to 14 days for GNR bacteremia

Dafna Yahav, Erica Franceschini, Fidi Koppel, Adi Turjeman, Tanya Babich, Roni Bitterman, Ami Neuberger, Nesrin Ghanem-Zoubi, Antonella Santoro, Noa Eliakim-Raz, Barak Pertzov, Tali Steinmetz, Anat Stern, Yaakov Dickstein, Elias Maroun, Hiba Zayyad, Jihad Bishara, Danny Alon, Yonatan Edel, Elad Goldberg, Claudia Venturelli, Cristina Mussini, Leonard Leibovici, Mical Paul, Bacteremia Duration Study Group, Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial, *Clinical Infectious Diseases*, Volume 69, Issue 7, 1 October 2019, Pages 1091–1098, https://doi.org/10.1093/cid/ciy1054

Prevalence of Pulmonary Embolism in Patients with Syncope

Journal of the American College of Cardiology, Vol 74, NO.6,
August 13, 2019: 744-754

Prevalence of PE in Syncope

- Syncope is very common – and establishing the etiology is challenging. PE needs to be included in the differential diagnosis
  - A study published in the New England Journal in 2016 suggested that 1 in 6 patients presenting with syncope has underlying PE (PESIT trial)
  - Another study published in the Archives of Internal Medicine suggested PE is over diagnosed

Prevalence of PE in Syncope

- BASEL IX study (BAsel Syncope EvaLuation Study) is a multicenter study in 13 countries including the US
- Patients over the age of 40, able to sign consent, presenting with syncope were recruited.
- Patients were excluded if they were already on anticoagulation
- All patients underwent a clinical assessment, vitals, lab testing including D-dimer, ECG.
- Additional testing including tilt table testing, echo, 24 hour ECG, implantable loop device were performed based on clinician decision

Prevalence of PE in Syncope

- Patients were evaluated for PE based on the following:
  - Measurement of D-dimer with age adapted cutoffs
    - This lab was drawn in a blinded fashion and all results were sent to a dedicated core laboratory
  - Wells score
    - Patients with Wells score less than or equal to 4 were considered unlikely for PE, greater than 4 were considered likely for PE

Modified Wells criteria: clinical assessment for pulmonary embolism

Clinical symptoms of DVT (leg swelling, pain with palpation)	3.0
Other diagnosis less likely than pulmonary embolism	3.0
Heart rate >100	1.5
Immobilization (≥3 days) or surgery in the previous four weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Probability	**Score**
Traditional clinical probability assessment	
High	>6.0
Moderate	2.0 to 6.0
Low	<2.0
Simplified clinical probability assessment*	
PE likely	>4.0
PE unlikely	≤4.0

Data from van Belle, A, et al. JAMA 2006; 295:172.

Prevalence of PE in Syncope

- Testing for PE (CTA-PE or V/Q scan) was performed in patients with high pre-test probability using Well's criteria or elevated D-dimers
  - Imaging criteria for PE were an intraluminal filling defect on CTPA or perfusion defect of at least 75% of a segment with corresponding normal ventilation on V/Q scan. Each scan was ready by a certified radiologist
- Follow up
  - Patients were contacted 12 and 24 months after discharge to determine the prevalence of PE during follow up.
  - Researchers also looked for re-hospilizations, outpatient treatments, and national death registries
- Outcomes
  - Prevalence of PE at presentation
  - Development of new PE and cardiovascular death during 2 year follow up

Prevalence of PE in Syncope - Results

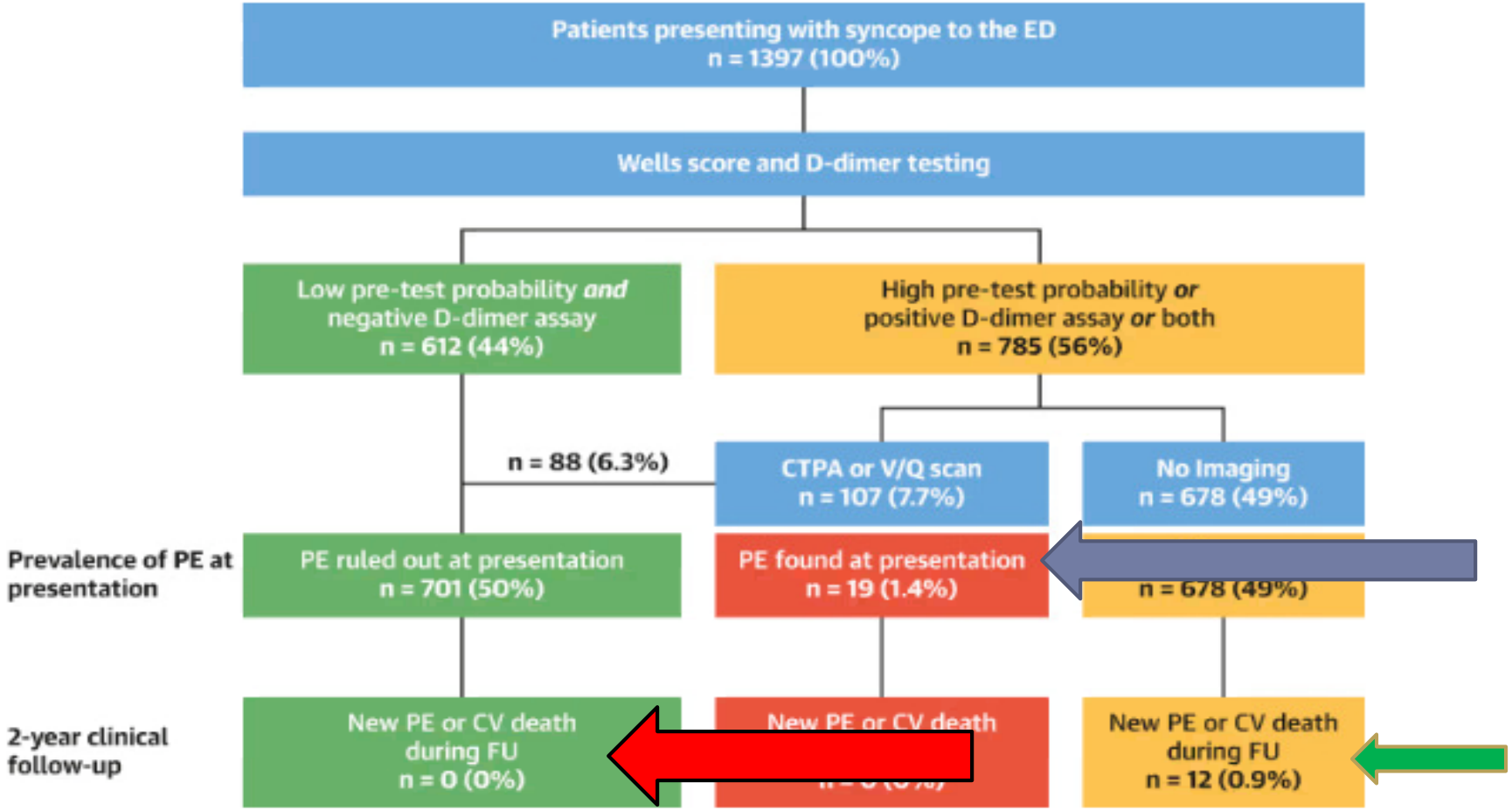


Figure 1

Prevalence of PE in Syncope - Results

- Subgroup of hospitalized patients
  - Overall prevalence of PE was **2.3%**, at 2 year follow up new incidence of PE and cardiovascular death was **0.9%**
  - In hospitalized patients with 1st syncopal event – incidence of new PE was **4.3%** and at 2 year follow up incidence of new PE and cardiovascular death was **0.8%**

Prevalence of PE in Syncope

- Limitations
  - Only patients stable enough to sign consent could be enrolled so patients who were hemodynamically unstable or with respiratory compromise weren't included
  - Median age was 69 (younger than 80 which was the median age for PESIT trial)
- Conclusions
  - It's reasonable to suggest PE workup should be tailored to patients in whom additional signs/symptoms such as dyspnea, signs of DVT, or signs on ECG at presentation (like RBBB) suggest PE as underlying cause

Prevalence of Pulmonary Embolism in Patients With Syncope. Patrick Badertscher, Jeanne du Fay de Lavallaz, Angelika Hammerer-Lercher, Thomas Nestelberger, Tobias Zimmermann, Marc Geiger, Orell Imahorn, Òscar Miró, Emilio Salgado, Michael Christ, Louise Cullen, Martin Than, F. Javier Martin-Sanchez, Salvatore Di Somma, W. Frank Peacock, Dagmar I. Keller, Juan Pablo Costabel, Joan Walter, Jasper Boeddinghaus, Raphael Twerenbold, Adriana Méndez, Boris Gospodinov, Christian Puelacher, Desiree Wussler, Luca Koechlin, Damian Kawecki, Nicolas Geigy, Ivo Strebel, Jens Lohrmann, Michael Kühne, Tobias Reichlin, Christian Mueller, for the BASEL IX Investigators. J Am Coll Cardiol. 2019 Aug, 74 (6) 744-754.

Patterns of Opioid Administration Among Opioid-Naïve Inpatients and Associations with Post-discharge Opioid Use

Annals of Internal Medicine, Volume 171, No. 2, 16 July 2019: 81-92

Patterns of Opioid Administration

- Retrospective cohort study using HER data from UPMC Health System and University of Pittburgh
- Inclusion criteria
  - Adults admitted to study hospitals who were opioid naïve (no documented opioid use in the inpatient and outpatient encounter databases in 12 months)
- Exclusion criteria
  - Admissions that were for deliveries
  - Admissions occurring <90 days from prior admit (only the first admission was included)
  - Those missing data (incomplete inpatient med records or those without outpatient encounter within 12 months before and after the admission
  - Patients who had opioid use in the 12 months prior to the admission (not naïve)

Patterns of Opioid Administration

- 3 outcomes were measured
  - Number of days on which any opioid was administered during the hospital stay, excluding post-op use (within 24 hours of surgery)
    - Information collected included timing of last opioid administration relative to discharge (in hours), location of first use (ER, ICU, ward), and use of non-opioid analgesics (NSAIDS or acetaminophen)
  - Opioid use at 90 days after discharge
  - Opioid use at 365 days after discharge
    - This data was self-reported use as they could not observe prescription fills in pharmacy using the outpatient database

Patterns of Opioid Administration

- Results
  - Generally, inpatients receiving opioids were more likely to be younger, female, and to have Medicaid or commercial insurance. They were also twice as likely to have been admitted for a surgical procedure. Comorbid musculoskeletal pain conditions were more common in stays with opioid use
  - Patients who received opioids received them for 67.9% of days
  - Non-opioid analgesics were rarely used before opioids
  - Receipt of opioids in the hospital was associated with a roughly 2 fold higher relative risk for outpatient use within 90 days (5.9% to 3.0%). Results were similar at 365 days.

Patterns of Opioid Administration

- Patterns associated with increased likelihood of outpatient use
  - Those given opioids for a higher percentage of stay
    - Those receiving opioids for 76-100% of their stay vs those receiving them for 1-25% of their stay were at higher risk for using opioids after discharge (RRR 1.25 – CI 1.09-1.43)
  - Those who received opioids during the last 12 hours of their hospital stay
    - Patients who received an opioid during the last 12 hours of their stay compared with those who did not receive an opioid for the last 24 hours of their stay had twice the risk for opioid use 90 days after discharge (RRR 2.02 – CI 1.83-2.23)
  - Those who received their first opioid in the emergency department (RRR 1.13 – CI 1.04-1.22)

Patterns of Opioid Administration

- The authors presented 4 key findings
  - Nearly half of opioid-naïve patients were given opioids in the hospital
    - They noted most of these patients received them before non-opioid analgesics
  - Any receipt of an opioid in the hospital was associated with roughly twice the probability of outpatient use after discharge
  - A large percentage of inpatients who received opioids received them for most of their stay and patients were frequently administered opioids within 12 hours of discharge
  - Patterns related to timing and duration of inpatient opioid administration were independently associated with increased probability of outpatient use up to 1 year after discharge

Patterns of Opioid Administration

- Limitations
  - Single health system
  - Observational study, at risk for confounders like history of substance use disorder, pain severity
  - Only looked back 12 months for opioid use – may have misclassified some patients as opioid naïve
  - No measurement of appropriateness of opioid use
  - Only looked at outpatient use recorded in outpatient records – didn't look at pharmacy fills or patients who received opioids illegally

Patterns of Opioid Administration

- Take away – receipt of any opioid in the hospital was associated with nearly twice the probability of continued outpatient use in opioid naïve patients

Donohue JM, Kennedy JN, Seymour CW, et al. Patterns of Opioid Administration Among Opioid-Naive Inpatients and Associations With Postdischarge Opioid Use: A Cohort Study. Ann Intern Med. [Epub ahead of print 18 June 2019]171:81–90. doi: 10.7326/M18-2864

Antipsychotics for Treating Delirium in Hospitalized Adults

Ann Intern Med. 3 September 2019 doi: 10.7326/M19-1860

Antipsychotics for Delirium

- Systematic review of randomized controlled trials and prospective observational studies to evaluate the benefits and harms of haloperidol and second-generation antipsychotics compared with placebo
- Study included 16 RCT and 10 observational studies
- Outcomes measured
  - Cognitive functioning
  - Hospital length of stay
  - Delirium severity
  - Sedation
  - Inappropriate continuation of antipsychotics
  - Safety (cardiac and neurologic as well as mortality)

Antipsychotics for Delirium

- Inclusion criteria
  - Studies that compared and antipsychotic with placebo or with another antipsychotic
  - Studies that evaluated outcomes relevant to the review
  - Observational studies with comparison groups that reported adverse events
- Exclusion
  - Studies without a validated instrument to diagnose delirium

Antipsychotics for Delirium - Results

- Effect on Cognitive Functioning
  - 3 studies reported on this, all with second-generation antipsychotics (olanzapine, risperidone, quetiapine) vs haloperidol
  - No difference in effect was reported
- Effect on Delirium severity
  - 12 studies reported on this using various instruments to document severity
  - Haloperidol vs placebo – inconsistent findings
  - Second-generation vs placebo – inconsistent findings
  - Second-generation vs haloperidol – no difference in severity

Antipsychotics for Delirium – Results Cont

- Hospital length of stay
  - 4 studies evaluated this outcome
  - Haloperidol vs placebo – no difference in outcome
  - Second-generation vs placebo – no significant difference in outcome
  - Second-generation vs haloperidol – no difference in outcome
- Inappropriate continuation of antipsychotics
  - No studies were found

Antipsychotics for Delirium – Results Cont

- Sedation
  - 11 studies evaluated this
  - Haloperidol vs placebo – no statistically significant difference in sedation related outcomes
  - Second-generation vs placebo – no effect on onset of sedation
  - Second-generation vs haloperidol – no difference in sedation related outcomes
- Delirium duration
  - 9 studies evaluated this
  - Haloperidol vs placebo – no effect on duration
  - Second-generation vs placebo – no effect on duration
  - Second-generation vs haloperidol – slightly longer delirium duration for second-generation antipsychotics

Antipsychotics for Delirium – Results Cont

- Mortality
  - 8 studies evaluated this, 1 other study evaluated palliative care patients
  - Haloperidol vs placebo – no effect. The study that evaluated palliative care patients reported a decreased survival for haloperidol
  - Second-generation vs placebo – no effect. The palliative care study reported a non-statistically significant decrease in survival for risperidone
  - Second-generation vs haloperidol – no effect on mortality

Antipsychotics for Delirium – Results Cont

- Cardiac effects
  - 10 studies
  - Haloperidol vs placebo – no difference in QT prolongation
  - Second-generation vs placebo – increased QT prolongation (RR 1.57 – CI 0.9-2.76)
  - Second-generation vs haloperidol – potentially important increase in QT prolongation and temporary increase in drug due to QT prolongation
- Neurologic effects (Extrapyramidal symptoms – EPS)
  - 22 studies
  - Haloperidol vs placebo – no increase in EPS
  - Second-generation vs placebo – no increase in EPS
  - Haloperidol vs second-generation – lower incidence of EPS in second-generation antipsychotics
  - No studies resulted in neuroleptic malignant syndrome

Antipsychotics for Delirium

- Discussion
  - No differences for haloperidol or second-generation antipsychotics, compared with placebo, in hospital length of stay, sedation, delirium duration, or mortality and insufficient evidence for the effect on cognitive function and delirium severity
  - Potentially harmful cardiac effects tended to occur more frequently in second-generation antipsychotics
  - The included studies did not evaluate the effect of antipsychotics on patient distress in-hospital or patient functioning after hospital discharge
  - Limitations – studies excluded patients with underlying cardiac or neurologic issues and were heterogeneous.

Antipsychotics for Delirium

- Bottom line – study authors don't recommend routine use of antipsychotics for treating delirium. But they also don't offer any alternatives

Nikooie R, Neufeld KJ, Oh ES, et al. Antipsychotics for Treating Delirium in Hospitalized Adults: A Systematic Review. Ann Intern Med. [Epub ahead of print 3 September 2019] doi: 10.7326/M19-1860

Questions??