Drug Interactions and Prevention of Adverse Events

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Learning Objectives

1. Use evidence-based criteria to evaluate for potentially adverse drug events, among patients receiving multiple medications.
2. Disseminate best practices in safety strategies to decrease ADEs from high priority medications in primary care.
3. Describe the different roles of different healthcare professions in managing patients’ medications safely and effectively.
4. Discuss the potential for misunderstandings and knowledge gaps between different professions, and the importance of continuing dialogue across the healthcare team.
5. Identify system, team, and individual strategies for reducing the frequency of adverse drug events.
Why is he confused?

72 yo with his: HTN, Depression, GERD, Herniated cervical disk

Meds:
- Amlodipine
- Lansoprazole
- Bupropion
- Tramadol
- Sertraline
- Aspirin

Labs:
- Sodium: 133 mEq/mL
- Blood urea nitrogen: 20 mg/dL
- Creatinine: 1.5 mEq/dL
- Glucose: 40 mg/dL
- Urinalysis: normal

Sex: Male
Live with his wife who has DM & is treated with metformin

AES POLL QUESTION

Which medication is the most likely cause of this man's altered mental status?

a. sertraline
b. bupropion
c. tramadol
d. lansoprazole
e. his wife’s metformin

RESULTS:

Tramadol vs Codeine
Tramadol was associated with increased risk of hospitalization due to hypoglycemia; risk is higher in 1st 30 days of use

Odds Ratio (confidence interval)

- case-control analysis: 1.52 (1.09 - 2.10)
- case-control analysis (1st 30 days of use): 2.61 (1.61 - 4.23)
- cohort analysis (1st 30 days of use): 3.60 (1.56 - 8.34)
- case-crossover analysis (1st 30d of use): 3.80 (2.64 - 5.47)

BACKGROUND

Adverse Drug Event (ADE)

Definition:
“an injury resulting from medical intervention related to a drug”

outpatient settings:
- 3.5 million physician office visits
- 1 million ED visits/year
- 125,000 hospital admissions/year

inpatient settings:
- 1/3 of all hospital adverse events
- 2 million hospital stays annually
- Prolong hospital stays by 1.7 to 4.6 days

Medication Use in 2006

General US population
- 82% reported use of rx, otc, supplements
- 29% ≥ 5 rx

Elderly ≥ 65 years
- 59% take 5 to 9 meds
- 19% take ≥ 10 meds

Rate of ADRs increases exponentially after use of 4 or more meds

Death & Serious Outcomes from ADEs

Wars ranked by American combat deaths

AES POLL QUESTION

True or False?
- More than 50% of ADR-related hospital admissions are preventable

Centers for Medicare & Medicaid

- Does not pay for hospital acquired conditions that are reasonably preventable; i.e. hypoglycemia

NATIONAL PLAN
National Action Plan for ADE Prevention

2 Key Objectives:

- Identify common, preventable, & measurable ADEs that may result in significant patient harm
- Align the efforts of Federal health agencies to reduce patient harms from these specific ADEs nationally

Magnitude of the problem: Anticoagulants

FDA Adverse Event Reporting System 2016

- 18,978 serious injuries
- 3,018 deaths

AES POLL QUESTION

In 2016, which anticoagulant accounted for the most injuries or deaths?

a. rivaroxaban
b. apixaban
c. dabigatran
d. warfarin
e. edoxaban

Magnitude of the problem: Diabetes Agents

In persons older than 65 years,

- insulin was implicated in 13.9% of emergent hospitalizations
- oral agents were implicated in 10.7% of emergent hospitalizations
Ms. Johnson is 65 years & has DM2 x 1 year; 3 months ago; she was prescribed Metformin 1000mg BID, Lisinopril/HCTZ for HTN, & aspirin 81mg QD

- HBA1c 7.5%
- BP 140/80 mmHg
- BMP wnl, eGFR > 60ml/min
- BMI 29

She reports an intermittent pain in her feet, but has difficulty localizing it. Ms. Johnson has CAD, for which she underwent a CABG 5 years ago.

AES POLL QUESTION

Which anti-hyperglycemic treatment option are you most likely to recommend?

a. Continue metformin monotherapy, same dose
b. Metformin + TZD (pioglitazone)
c. Metformin + DPP-4 inhibitor (Januvia, Tradjenta, onglyza)
d. Metformin + GLP-1 agonist (Byetta, Victoza, Trulicity)
e. Metformin + long-acting insulin (Lantus, Levemir)

Don’t medicate to achieve tight glycemic control in older adults. Moderate control is generally better.

- There is no evidence that using medications to achieve tight glycemic control in older adults with type 2 diabetes is beneficial.
- Among non-older adults, except for reductions in myocardial infarction and mortality with metformin, using medications to achieve glycated hemoglobin levels less than 7% is associated with harms, including higher mortality rates.
- Given the long time frame to achieve theorized microvascular benefits of tight control, glycemic goals should reflect patient goals, health status, and life expectancy.

Magnitude of the problem: Opioid Agents

Pain affects more Americans than:
Diabetes + Heart Disease + Cancer combined

- US spent $8.4 Billion in opioids in 2010
- 16,651 opioid overdose deaths
- 420,000 ED visits


PRIMARY CARE PLAN

Reducing ADEs from Anticoagulants, Diabetes Agents & Opioids in Primary Care

- “ADEs across inpatient & outpatient settings are common, clinically significant, preventable & measurable for high priority medications”
  - Anticoagulants
  - Diabetes agents
  - Opioids
Reducing ADEs in Primary Care:

- Identify risk factors for ADEs
- Translate them to Clinical Quality Measures (CQM)
- Supplement with "meaningful use" CQMs
- Gather provider input
- Test a "Community Engaged" approach

Wessell, Andrea M
Medical University of South Carolina

RISK FACTORS

Risk Factors for ADEs: General

- Advanced age
- Polypharmacy
- Decreased Renal Function
- Low Health Literacy

Risk Factors for ADEs: Bleeding due to Anticoagulants

- Concurrent use of >1 antithrombotic (warfarin, aspirin)
- History of stroke or GI bleed
- NSAID use with anticoagulants
- Antibiotic use with anticoagulants
- Amiodarone use
- Dietary changes affecting vitamin K


Risk Factors for ADEs: Hypoglycemia due to Antidiabetic Agents

- insulin use / sliding scale
- oral hypoglycemic medication use
- decrease in oral intake while on antidiabetics
- history of severe hypoglycemia
- insulin duration of more than 10 years
- Low BMI
- Cachexia
- CHF
- Age


Risk Factors for ADEs: Respiratory Depression/Delirium due to Opioids

- PRN or routine use of opioid medication
- Opioid naive
- Opioids + sedatives or + other opioids
- History of opioid abuse
- Opioid tolerance
- Severe pain
- Low fluid intake/dehydration
- Low body weight
- History of head injury, traumatic brain injury, or seizures

EVIDENCE BASED PRACTICE

3 Evidence-Based Practices that can be immediately implemented

- Medication reconciliation
- Teach Back
- Focused anticoagulation clinics

Medication Reconciliation

"Evidence supporting the need for and the value of medication reconciliation is strong. More than half of all medication errors occur at the interfaces of care."

- Without reconciliation, 67% of patients were found to have medication errors in their histories
- Chosen as a "proven" change or a "safety goal" by:
  - Institute for Health Care Improvement ("100K Lives")
  - Joint Commission on Accreditation of Healthcare Organizations (JCAHO)

Evidence supporting the need for and the value of medication reconciliation is strong. More than half of all medication errors occur at the interfaces of care.

http://www.ihi.org/education/ihischool/learningmodules/HRMP/medicationreconciliation.htm

Medication Reconciliation

- In hospitalized patients:
  - May reduce ED contacts by 27%
  - NNT = 37 for low risk population
  - NNT = 12 for high risk population

Cochrane Database of Systematic Reviews, Feb 20, 2016

Pharmacotherapy: A Pathophysiologic Approach, 9th

AES POLL QUESTION

What percent of patients forget what the doctor told them when they leave the office?

a. 20 %  b. 40 %  c. 60 %  d. 80 %  e. 90 %

Teach Back

up to 80% of the medical information patients are told during office visits is forgotten immediately.... and nearly half of the information retained is incorrect.

Teach Back can:
- Improve patient understanding & adherence.
- Decrease call backs & cancelled appointments.
- Improve patient satisfaction & outcomes.

Anticoagulation Clinics

3.5. (Best Practices Statement) We suggest that health-care providers who manage oral anticoagulation therapy should do so in a systematic and coordinated fashion, incorporating:
- patient education
- systematic INR testing
- tracking
- follow-up
- & good patient communication of results & dosing decisions

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3278055/

Anticoagulation Clinics

- focused anticoagulation clinics
  - higher time in therapeutic range
  - more INR values at goal
  - decreased ED visits/hospital admissions
  - decreased cost $800-$1600 per pt per year

Role of anticoagulation clinics for NOACs

- identify appropriate patient candidates
- transition safely from older to newer agents
- monitor patients during interruption of therapy
- dose accurately for age & renal function
- provide patient education
- general coordination

AES POLL QUESTION

What percent of patients are enrolled in anticoagulation clinics?

a. 20 %
b. 40 %
c. 60 %
d. 80 %
e. 90 %
Suggested Process Measures

- % of patients on insulin with BG <80 mg/dl at least once
- % of patients receiving opioids who receive an opioid risk assessment prior to 1st dose
- % of patients receiving opioids who regularly receive a formal assessment

Driver Diagram

Visually demonstrates the causal relationship between:
- your change ideas
- secondary drivers
- primary drivers
- & your overall aim

Suggested Process Measures

- % of patients/families that can correctly state risks, benefits & alternatives in their own words
- % of patients who opt for a different option given the explanation of risks/benefits
- % of patients who successfully performed a “teach-back” at discharge counseling
**How to Avoid ADEs: Barriers**

- **Provider:**
  - Fear of loss of autonomy
- **Patients:**
  - Long distance for patients
- **System:**
  - Concern regarding benefits, cost, training
- **Economic**
  - Challenges in payment/coverage for these services

**Action Planning**

- Assess your organization
- Start by:
  - Searching for INRs > 5
  - Glucoses < 50 mg/dL
  - Naloxone use
  - Engage staff by asking their ideas
  - Find champions (physicians, nurses, pharmacists, administrative)
- Start with small changes

**Best Practices**

- Greater Detroit Area Health Council
- Integrated Healthcare Association
- Maine Quality Counts
- North Carolina Healthcare Quality Alliance
- University of California, Los Angeles
- Washington Health Alliance
- Wisconsin Collaborative for Healthcare Quality

**What is Your Professional Role?**

67 yo with HTN, GERD, Afib, presents with fatigue, cough, HA, DOE, fever

Meds:
- Lisinopril
- Flomax

Labs:
- Sodium: 133 mEq/L
- Blood urea nitrogen: 20 mg/dL
- Creatinine: 1.0 mg/dL
- Glucose: 98 mg/dL
- INR=2.5

Notes:

3 days later with GI bleed

- Clarithromycin
- Lisinopril
- SWAT
- Esomeprazole pm
- Warfarin pm

Gives pt Rx
- “do you have any?”

3 days later with GI bleed

“alert fatigue”
Professional Roles

- Patients
- Patient Advocates
- Providers (MD, PA, NP, etc)
- Nurses / MA
- Pharmacists
- Technicians
- Administrators
- Human Resources
- Legal

Safe Medicine Management

Most Dangerous stages of medicine management:

1. Prescribing stage
2. Administration stage

AES POLL QUESTION

All of these medication have been taken off the market because of drug interactions EXCEPT?

a. Terfenadine (Seldane)
b. Mibefradil (Posicor)
c. Astemizole (Hismanal)
d. Cisapride (Propulsid)
e. Ketoconazole (Nizoral)

INTERACTIONS

Clinically Significant Drug Interactions

- Warfarin +
  - cipro
  - metronidazole
  - clarithromycin
  - TMP / SMX
- Sildenafil + nitrates
- Fluoroquinolones + cations
- SSRI + tramadol
- SSRI + sumatriptan
- OCPs + rifampin
- Simvastatin + Amlodipine (don't exceed 20mg simva)

Simvastatin Restrictions

- do not exceed 40mg
- 80mg increases myopathy x 7 & only decreases LDL by 6% more
- Don’t exceed 20 mg with amlodipine or ranolazine
- Don’t exceed 10 mg with amiodarone, diltiazem, or verapamil
- Don’t use simvastatin at all with gemfibrozil or strong CYP3A4 inhibitors...itraconazole, clarithromycin, protease inhibitors, etc.
FDA Safety Warnings

- canagliflozin, dapagliflozin (strengthened warning of AKI)
- saxagliptin, alogliptin (increased hospitalizations due to HF)
- fluoroquinolones
  - “associated with disabling & potentially permanent side effects of the tendons, muscles, joints, nerves, & central nervous system that can occur together in the same patient”
- Zecuity Patch (sumatriptan) – suspended due to skin burns & scars
- Pregnancy risk with progestin-releasing implants in HIV women treated with efavirenz
- tainted supplement products
  - “Man of Steel” (sildenafil)
  - “Xplode” (sibutramine)

Medication Safety Information Resources

- Institute for Safe Medication Practices: www.ismp.org
- Agency for Healthcare Research & Quality: www.ahrq.gov
- Centers for Medicare & Medicaid Services: www.cms.gov
- The Joint Commission: www.jointcommission.org
- National Coordinating Council for Medication Error Reporting & Prevention: www.nccmerp.org
- Institute of Medicine of the National Academies: www.iom.edu

Institute of Clinical Pharmacology www.icspharmacology.org

Pharmacotherapy: A Pathophysiologic Approach, 9e

How to Avoid ADEs: Summary

- Establish a multi-disciplinary collaborative practice
- Educate patients
- Be aware of “black box” warnings
- Pay attention to drugs with a narrow therapeutic index
- Avoid the “Pharmacy Cascade”
- Remain vigilant of drug-drug interactions which can be serious & life-threatening
- Stay up-to-date
- Encourage patients to disclose all medications/supplements
- Develop strategies to prevent ADEs

Centers for Medicare & Medicaid

- Recommendations:
  - Follow guidelines
    - CMS refers to evidence-based guidelines
  - Be familiar with complications CMS will deny reimbursement
  - Re-evaluate & update your practice based on new information

Can you recognize the teaspoon?

Marking Syringe Helps Parents Give Correct Dose

Take Home Messages

Questions

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